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American Heart Journal

VOL. 48 AUGUST, 1954 No. 2

Original Communications

UNUSUAL MUSICAL MURMURS OF ANTERIOR CUSP AORTIC REGURGITATION

REPORT OF TEN CASES

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GALVESTON, TEX.

GREAT emphasis has always been placed on exhaustive clinical examination of the heart by the teachers in our cardiovascular unit. We never accepted Mackenzie's dictum that the myocardium and mechanism are all important and that the incompetent valve is of little significance. One of us took this stand in 1928 when accorded the privilege of rewriting Mackenzie's section in *Oxford Medicine*[1] and in the first to the fourth editions of *Diseases of the Heart and Arteries*.[2] We have held to this in spite of criticism of what was considered an unwarranted emphasis and space alloted to discussion of valvular lesions. The study in minute detail of the character, localization, propagation, and transmission of heart murmurs is now again being accorded much attention. The new interest in exact clinical diagnosis of valvular lesions has developed with the advances in the surgical treatment of scarred, dysfunctioning heart valves.

In our teaching of physical diagnosis we insist upon our students presenting physical evidence not only of what heart valve is involved but also of what cusp is most extensively damaged. As a result the physical exploration of our patients has been extensive, and we have had a wide experience in unusual murmurs. We realize fully that we have probably overemphasized the rarities, and we have used the eponyms designating murmurs more than we should. We feel that the description of every murmur should precede the name or names of the person who is recorded as having first described it.

From the Pathology and Cardiovascular services of the University of Texas Medical Branch, Galveston, Tex.

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HISTORY

Musical murmurs of aortic insufficiency were first described by Hodgkin in 1829,[3] although he gave credit to Key for the original observation in 1827. He pointed out that occasionally under unusual circumstances the typical high-pitched blowing diastolic murmur may assume a musical quality. The intensity of such a musical aortic diastolic murmur may be so great that it is heard at all valve areas and even by the patient. However, Elliotson in 1830[4] maintained that Bertin[5] had noted such findings as early as 1824. Strangely, this striking murmur has received little mention in the literature until recent years. Bellet and his co-workers[6] focused attention on the musical aortic diastolic murmur by analyzing a series of such cases in 1939 and have recently published a second series.[7] Other investigators[8-13] have similarly contributed, generally by single case reports.

The musical aortic diastolic murmur of Hodgkin-Key has been recognized by two of us in each of our ten cases, and we suspected the presence of a characteristic lesion of the right anterior aortic cusp. The recognition carried with each diagnosis the inference as to the etiologic factor and the poor prognosis in each instance. Careful follow-up in our observed cases with necropsy data has enabled us to affirm the accuracy of our clinical conclusions.

ETIOLOGY AND PATHOGENESIS

The musical aortic diastolic murmur variously described as "cooing," "buzzing," "humming," or "sawing" (bruit de scie) occurs in the majority of cases in patients with syphilitic aortic valvulitis. The peculiar musical quality is correlated with an eversion or rupture of an aortic cusp, particularly the right anterior cusp. The vibration of the everted or retroverted cusp in the path of the flowing regurgitant stream could well produce the unusual acoustical quality.

In most cases of syphilitic aortitis there occurs a dilatation of the aortic ring and ascending aorta and widening of the commissures between the aortic cusp. A thickening of the edges develops, tending to produce a lowering of the cusp margin. The tensile strength of the cusp is diminished by the fraying of the elastica and collagenous tissue alteration. Apparently, in some cases these factors predispose to an eversion of the valve when subjected to the stress of the altered vascular flow produced by the existing aortic insufficiency.

Occasional cases have been ascribed to rheumatic valvular lesions or to bacterial endocarditis. The musical quality in rheumatic valvulitis may be the result of eversion, or a freely movable sessile or nodal vegetation attached to the approximating surface of the leaflet.

In rare instances, the musical murmur has been produced by a traumatic or spontaneous rupture of an aortic cusp. True laceration or tearing of an aortic leaflet has generally been secondary to the presence of a marked weakening, particularly about the commissures, where the rupture in syphilitics has tended to occur. In the nonsyphilitic cases the valvular area around the tear has usually been found to be markedly thinned.

Pathology.—Regardless of etiology the majority of cases of musical aortic diastolic murmurs have shown a gross deformity of the right anterior cusp. Although this has usually been an eversion or retroversion, a rupture can produce the murmur, particularly if the free edge of the torn leaflet tends to vibrate. In the syphilitic cases there occur other gross characteristics of the slow aortic wall infarction, such as pearly or porcelain plaques, cigarette paper wrinkling of the intima, widening of the commissures, and rolling of the valve edges. Patients with rheumatic valvulitis or bacterial endocarditis may present eversion or a vegetation capable of vibration. In those due to traumatic laceration alone, there is demonstrable a thin section of the aortic valve free to vibrate in the regurgitant stream.

Microscopically, the aortic valves in the syphilitic process show a loss of the elastica, an abnormal fibro-collagenous tissue with superimposed chronic inflammatory reaction, and syphilitic aortitis. The nonsyphilitic lesions microscopically are characteristic of the parent disease, such as bacterial endocarditis or rheumatic valvulitis.

THE PRESENT STUDY

Ten patients with musical aortic diastolic murmurs have been observed at the University of Texas Medical Branch within the past 12 years. The analysis of these cases forms the basis for this report.

A summary of the pertinent features of the entire series is given in Table I. The ages varied from 33 to 70, and all of the cases occurred in Negroes. Nine

TABLE I. SUMMARY OF CASES*

AGE	SEX	ECG	DURATION OF LIFE AFTER MURMUR ONSET	CUSP INVOLVED BY PROCESS	PATHOLOGY
49	Male	Incomplete left bundle branch block, atrial fibrillation	5 days	Right anterior cusp	Eversion and laceration
36	Male	Left bundle branch block	7 months	Right anterior cusp	Eversion
39	Male	Left ventricular hypertrophy	4 months	Left anterior cusp	Eversion
42	Male	Left ventricular hypertrophy	6 months	Right anterior cusp	Eversion
56	Male	Left bundle branch block, atrial fibrillation	4 months	Right anterior cusp	Eversion
70	Male	Not abnormal	3 weeks	Right anterior cusp	Eversion
55	Male	Left ventricular hypertrophy	18 months	No post-mortem	
33	Male	Left ventricular hypertrophy	9 months	No post-mortem	
44	Male	Incomplete left bundle branch block, atrial fibrillation	?, day	No post-mortem	
50	Female	Left ventricular hypertrophy, atrial fibrillation	5 months	No post-mortem	

*All of the cases were of syphilitic etiology; all were Negroes; and all presented symptoms of congestive failure.

of the ten patients were males. All of our cases were of syphilitic etiology, and each presented symptoms and signs of congestive failure. Electrocardiograms were taken on all of these patients, and in only one was there no definite evidence of abnormality. The tracings showed the changes to be expected from an overload on the left ventricle in syphilitic aortic insufficiency. There were complete left bundle branch block in two patients, incomplete left bundle branch block in two, and left ventricular hypertrophy in five. An unusual finding was the presence of atrial fibrillation in four cases, in one of which it was terminal.

It is significant that five of the six necropsied cases showed eversion of the right anterior valve, while the remaining one demonstrated an eversion of the left anterior cusp. In one of the cases involving the right anterior leaflet, a laceration of the valve at the commissure was noted.

The prognosis was generally poor, nine of the ten patients dying within nine months, and one remaining alive for eighteen months. In one patient who died within nine months, the musical quality of the murmur disappeared before death; however, no autopsy was obtained.

CASE REPORTS

CASE 1. M. T., 49-year-old Negro was admitted with a history of progressive dyspnea, dependent edema, and ascites for 6 months. Blood pressure was 200/80 mm. Hg (bilaterally), and pulse was regular at a rate of 90 per minute. The heart was enlarged to the left, with point of maximal impulse in the fifth intercostal space 12 cm. to the left of the midsternal line. A systolic thrill was felt to the right of the upper sternum, and harsh systolic and blowing diastolic murmurs were heard at the aortic area. There were evidences of right and left ventricular failure.

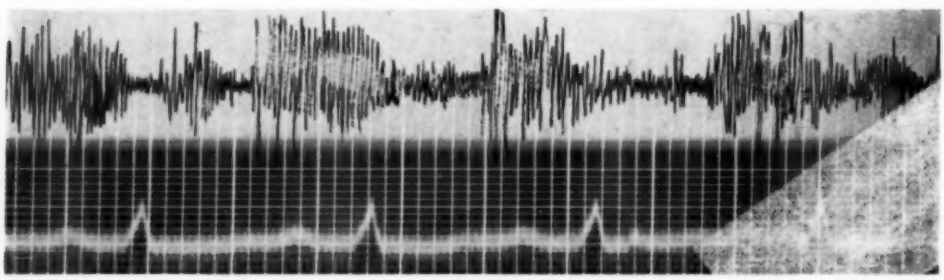

Fig. 1.—Phonocardiogram (Case 1) shows a loud musical diastolic murmur which obscures the second sound. This murmur has a short crescendo initial phase but is then decrescendo. There is also a systolic murmur of moderate intensity. Retouched by G. W. Newman.

Seven days following admission, the patient suddenly developed severe pulmonary edema. At this time the aortic diastolic murmur was noted to have become high-pitched and musical (Fig. 1). An electrocardiogram showed atrial fibrillation with incomplete left bundle branch block. Teleradiogram revealed conspicuous cardiomegaly and congestion of the lung fields. Despite supportive measures and therapy for cardiac decompensation, the patient expired 5 days later. The patient denied venereal disease, but the quantitative Kahn test was positive in a titer of 1:1,280. The clinical diagnosis was that of eversion of the right anterior aortic cusp.

Post-mortem findings: The heart weighed 670 grams, and the aortic valvular ring measured 9 cm. The final pathologic diagnoses were: (1) syphilitic aortitis and valvulitis; (2) laceration and eversion of the right anterior aortic cusp (Figs. 2 and 3); (3) left ventricular hypertrophy and dilatation of both ventricles; (4) pulmonary edema; and (5) anasarca.

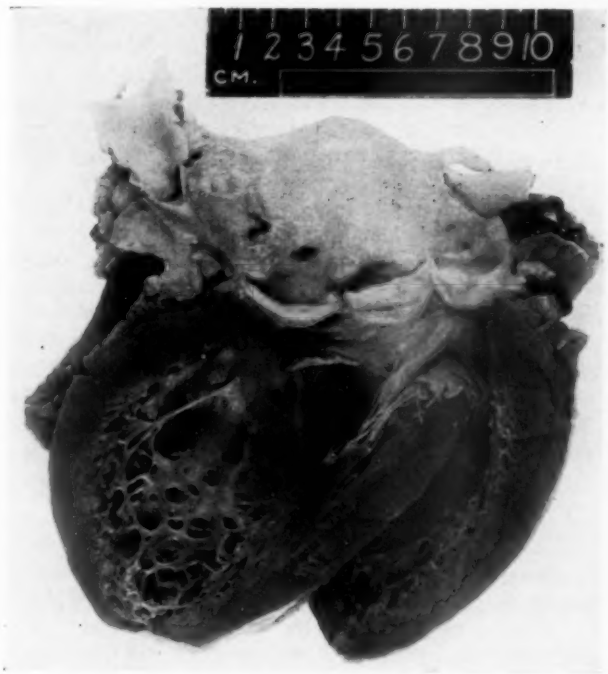

Fig. 2.—A gross photograph of the heart (Case 1) showing the laceration and eversion of the right anterior cusp.

Fig. 3.—Photomicrograph. Side view presenting the eversion of the right anterior cusp (Case 1).

CASE 2. C. C., 36-year-old Negro, gave a history of pain of an anginal character associated with shortness of breath and pedal edema for 8 months. On his first admission the blood pressure was 150/65 mm. Hg, and the heart was enlarged to the left with point of maximal impulse in the sixth intercostal space at the anterior axillary line. There was a high-pitched musical diastolic murmur of "cooing" quality in the aortic area, transmitted unchanged to the apex. There were moist râles at the lung bases, hepatomegaly, and pedal edema. The patient responded poorly to digitalis and diuretics and was discharged slightly improved.

One month later he was readmitted in severe congestive heart failure with hemoptysis due to pulmonary infarctions. The musical murmur of the regurgitation through a right anterior cusp was again heard and remained present until his death 7 months after its onset. Electrocardiograms revealed left bundle branch block. Teleradiogram showed cardiomegaly and multiple pulmonary infarctions. The patient had had a primary syphilitic lesion 10 years before with inadequate therapy, but during hospitalization serologic tests for syphilis were negative.

Post-mortem findings: The heart weighed 900 grams, and the aortic valvular ring measured 9.5 cm. The final anatomic findings confirmed the clinical diagnoses and were: (1) syphilitic aortis, valvulitis with eversion of the right anterior aortic cusp; (2) cardiomegaly and dilatation; (3) multiple pulmonary infarctions; (4) bronchopneumonia; (5) pulmonary edema.

CASE 3. E. W., 39-year-old Negro, was hospitalized eleven times during the final 2 years of his life because of persisting shortness of breath due to left ventricular failure. He presented evidences of aortic insufficiency, and 4 months before death there was a sudden striking increase in dyspnea and a conspicuous change in the aortic diastolic murmur, which became musical in character. On his final admission the blood pressure was 158/48 mm. Hg, and there was marked cardiac enlargement. Numerous basal râles were heard, and hepatomegaly and edema were noted. The previously heard musical aortic diastolic murmur was still present. Electrocardiograms showed left ventricular hypertrophy, and the teleradiogram showed marked cardiac enlargement. The patient died in marked congestive failure. He gave a history of penile lesion 5 to 6 years previous to the onset of heart failure, and at the time of hospitalization his serology was positive.

Post-mortem findings: The heart weighed 860 grams, and the aortic valvular ring measured 8.5 cm. The final anatomic diagnoses were: (1) syphilitic aortitis and valvulitis with eversion of the left anterior cusp; (2) cardiomegaly and dilatation of both ventricles; (3) mural thrombus formation in right atrium; (4) multiple pulmonary infarctions; (5) bronchopneumonia; (6) anasarca.

CASE 4. A. R., 42-year-old Negro, was admitted for surgery because of a strangulated inguinal hernia. He had been treated for the previous 6 months for severe congestive heart failure associated with a musical "humming" diastolic murmur. At the time of terminal hospitalization his blood pressure was 162/50 mm. Hg, and the point of maximal impulse was in the sixth intercostal space in the anterior axillary line. The musical aortic diastolic murmur was again heard. On the sixth postoperative day he developed a wound infection, and he expired suddenly on the tenth postoperative day from a massive pulmonary embolus.

An electrocardiogram had revealed left ventricular hypertrophy, with chest film showing marked cardiac enlargement. The patient gave a history of syphilis 20 years previously, and at the time of hospitalization his serologic test for syphilis was positive.

Post-mortem findings: The heart weighed 580 grams, and the aortic valvular ring measured 9 cm. The final anatomic diagnoses were: (1) syphilitic aortitis and valvulitis with eversion of the right anterior cusp; (2) cardiomegaly and ventricular dilatation; (3) infection of surgical wound in inguinal region; (4) pulmonary embolism; (5) arteriolar nephrosclerosis.

CASE 5. E. H., 70-year-old Negro, was admitted with the chief complaint of increasingly severe epigastric discomfort for 3 weeks. There was also marked dyspnea. Examination revealed signs of superior vena caval obstruction. The blood pressure was 175/75 mm. Hg, and a tracheal tug was demonstrated. The heart was enlarged to the left, and there was conspicuous widening of the retro-manubrial dullness. A cooing aortic diastolic murmur was heard for the 3 weeks prior to his death. Electrocardiogram showed no definite abnormality. Fluoroscopy

demonstrated a pulsating fusiform aneurysm in the superior mediastinum. Although no positive history of syphilis was elicited, the serologic test was positive.

Post-mortem findings: The heart weighed 480 grams, and the aortic valvular ring measured 10 cm. Final pathologic diagnoses were: (1) aneurysm of ascending aorta with rupture into the superior vena cava; (2) syphilitic aortitis and valvulitis, with eversion of the right anterior aortic cusp; (3) cardiomegaly and ventricular dilatation; (4) pulmonary edema; (5) edema of face, arms, neck, and chest walls (superior vena caval obstruction).

CASE 6. W. J., 56-year-old Negro gave a history of repeated bouts of congestive failure characterized by dyspnea, weakness, and edema for 2 years. The blood pressure was 160/70 mm. Hg. The heart was markedly enlarged to the left, and a diastolic thrill was present over the aortic area. A musical aortic diastolic murmur was heard. Final admission was because of a massive left cerebral hemorrhage, and the patient expired 4 days later. An electrocardiogram showed atrial fibrillation and left bundle branch block. Teleradiogram confirmed the marked cardiac enlargement. The patient gave a history of numerous nontreated penile ulcers years previously, and at the time of terminal admission the serologic test for syphilis was positive.

Post-mortem findings: The heart weighed 740 grams, and the aortic valvular ring measured 9 cm. The final anatomic diagnoses were: (1) syphilitic aortitis and valvulitis with eversion of the right anterior aortic cusp; (2) cardiomegaly and ventricular dilatation; (3) pulmonary edema and bronchopneumonia; (4) anasarca; (5) arteriolar nephrosclerosis; (6) left intracerebral hemorrhage.

CASE 7. C. F., 55-year-old Negro, was admitted to the hospital with shortness of breath for 3 weeks. He described the onset of a "buzzing" in his chest 10 days before admission. He was orthopneic with ascites and dependent edema. There were Argyll-Robertson pupils. The blood pressure was 146/60 mm. Hg, and the pulse was of the water-hammer type. Cardiomegaly was demonstrated, and there was heard a musical aortic diastolic murmur. Electrocardiogram showed left ventricular hypertrophy. This patient was hospitalized four times during his last 18 months. During this time, the musical aortic diastolic murmur was consistently present, and he had intractable heart failure, from which he finally died. No history of a penile lesion was elicited; however, the serologic test for syphilis was positive. Post-mortem examination was refused.

CASE 8. L. H., 33-year-old Negro, was admitted with symptoms and signs of right and left ventricular failure. Twelve days prior to admission he noted a "buzzing" in his chest. The blood pressure was 170/30 mm. Hg. The heart was enlarged to the left, and a musical aortic diastolic murmur was heard. The heart failure was relieved, and he was discharged.

After his second hospital admission a month later it was found that the aortic diastolic murmur had lost its musical character. The electrocardiogram showed left ventricular hypertrophy. He gave a history of a penile lesion 20 years before, and the serologic test for syphilis was positive. The patient expired at home nine months following the onset of the musical murmur. No post-mortem examination was done.

CASE 9. F. H., 44-year-old Negro, gave a history of heart failure for the previous 4 years. On the final admission he was in severe congestive failure with cyanosis and marked pulmonary and peripheral edema. Blood pressure at this time was not obtainable. The heart was markedly enlarged to the left. Auscultation revealed a musical aortic diastolic murmur transmitted down the left border of the sternum. An electrocardiogram showed atrial fibrillation and incomplete left bundle branch block. Teleradiogram showed a greatly enlarged cardiac silhouette and pulmonary congestion. This patient had a history of previous syphilis, and on his final admission the serologic test was positive. He expired the day after admission. Post-mortem examination was refused.

CASE 10. L. J., 50-year-old Negro woman, gave a history of paroxysmal nocturnal dyspnea associated with pulmonary edema for one month. The patient was a known diabetic and was admitted in a comatose state. The blood pressure was 205/65 mm. Hg, and the pupils were non-

reactive to light. Cardiomegaly, hepatomegaly, and dependent edema were present. A loud aortic musical diastolic murmur was heard. Althouth the diabetic acidosis was controlled, the degree of congestive failure increased. An electrocardiogram showed atrial fibrillation and left ventricular hypertrophy. Teleradiogram showed cardiomegaly to the left, congestion of the lung fields, and pulmonary infarction. Although no positive history of venereal disease was obtained, the serologic test for syphilis was 4-plus. The patient expired 5 months following admission. Post-mortem examination was not done.

DISCUSSION

An analysis of the etiologic distribution in previous reports is presented in Table II with the findings in the present series. Although most of the cases were due to syphilis, twelve of the forty-eight collected cases were found to have rheumatic aortic valvulitis, bacterial endocarditis, or traumatic rupture. The incidence of rheumatic valvulitis is less in the South than in the North, and this may be the reason why we observed no such cases. Since bacterial endocarditis tends to occur on a rheumatic valvulitis most commonly, this may also be the reason why none of our cases were of that etiology. With the striking present decline in incidence of syphilitic aortitis[14] and decrease in acute rheumatic fever,[15] it is anticipated that patients with musical aortic diastolic murmurs will become even more of a rarity.

TABLE II. ANALYSIS OF ETIOLOGY

AUTHOR	CASES	SYPHILIS	RHEUMATIC	SBE	RUPTURE
Bellet et al.—1939	11	10	1		
Nichols—1940	5	5			
Bushong—1947	2				2
Wells—1949	2		2		
Gelfand and Bellet—1951	18	11	2	3	2
Present series—1954	10	10			

SBE—Subacute bacterial endocarditis.

The right anterior cusp is by far the most often involved. In Bellet's report of 1939[6] all of the six autopsied cases showed syphilitic eversion of the right anterior cusp, but one also presented an eversion of the posterior leaflet. In the five necropsied cases reported by Gelfand and Bellet in 1951,[7] all were due to deformity of the right anterior cusp, two being eversion secondary to syphilitic aortic valvulitis, two traumatic rupture, and one eversion was secondary to rheumatic valvulitis. In three autopsied cases cited by Nichols,[16] all were of syphilitic etiology, and two were due to pathology of the right anterior cusp while one involved the posterior leaflet. Five of our six autopsied cases showed eversion of the right anterior valve, and one of the left. The high incidence of right anterior cusp involvement may be due to the fact that the aorta in this region receives little support from contiguous structures and that the column of blood in the aorta exerts its greatest force upon the right anterior leaflet during closure.

Atrial fibrillation was recorded in four of our patients, although it is generally stated to be uncommon in syphilitic aortic insufficiency. However, we have

noted it to be more frequent than generally supposed, even in patients not in congestive heart failure.

The development of an eversion of the aortic cusp imposes a sudden, serious change in the circulatory hemodynamics. There is an immediate increased load upon the left ventricle, and the diastolic filling of the coronary arteries is further impaired. This is particularly true of the right coronary artery, which is deprived of its valve shelf when the right anterior cusp is everted. A sudden adverse increase in the symptoms was noted by all of our patients upon the development of the eversion, signaled by the appearance of the diastolic musical murmur. In several cases the syndrome inaugurated was manifested by an acute left ventricular failure; in several other cases by symptoms of coronary insufficiency. In two the time of onset was determined by the patient becoming aware of an audible murmur.

We feel that in syphilitic aortitis the appearance of a musical diastolic murmur is of grave moment. Nine of our ten patients died within nine months of the observation of the murmur. In 1939, Bellet and associates[6] recorded the longevity following eversion from six weeks to three years, but in 1951 favorably modified this prognosis. At that time the longest follow-up was six years, and in some cases the musical quality had disappeared (in acute bacterial endocarditis). It would seem that the prognosis is not quite as grave in the nonsyphilitic cases.

SUMMARY

1. Ten patients with musical aortic diastolic murmurs have been observed within a 12-year period. All occurred in the Negro race, and nine were males. All were of syphilitic etiology.

2. Electrocardiograms were abnormal in nine patients with four showing atrial fibrillation.

3. Appearance of the murmur was generally followed by marked adverse change in the circulatory status and gravely altered the prognosis.

4. In the six necropsied cases, eversion of the right anterior cusp was found in five, and of the left anterior cusp in one. A laceration complicated one of the cases showing an eversion of the right anterior leaflet.

5. Nine of the patients died within nine months, and the remaining one lived 18 months. In one case the musical quality of the murmur disappeared prior to death.

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BLOOD PRESSURE AND RENAL HEMODYNAMIC RESPONSES TO ARAMINE AND THE ALTERATIONS OF THESE RESPONSES BY ADRENERGIC BLOCKADE WITH DIBENZYLINE

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NOREPINEPHRINE produces marked renal vasoconstriction in both dogs and man when given by continuous intravenous infusion.[1-4] Since this would be an undesirable action under certain conditions it seemed worthwhile to observe the renal hemodynamic response to Aramine (levo-1-(m-hydroxyphenyl)-2-amino-1-propanol), a synthetic sympathomimetic amine and to compare these observations with the renal hemodynamic response to norepinephrine. Concurrent observations were made on the effect of this agent on blood pressure elevation and on water and electrolyte excretion. A second objective in the current study was to evaluate the renal hemodynamic response to Aramine following adrenergic blockade. Because of the sharp reduction in blood pressure when norepinephrine is infused in the presence of adrenergic blockade it has not been feasible to use this agent for evaluating the existence of blockade of the renal vessels, since one can not be sure whether the reduction of renal blood flow is associated with the fall in systemic blood pressure or is a result of renal vasoconstriction produced by the norepinephrine. The use of Aramine circumvents this objection since the administration of Aramine following adrenergic blockade is not associated with blood pressure reversal as in the case of norepinephrine.

METHODS

The study was divided into two parts. In the first part, nine mongrel dogs were given Aramine alone. In the second part, the effect of adrenergic blockade on the response to Aramine was studied in ten dogs and the effect of ganglionic blockade with hexamethonium in three others. All of the dogs were anesthetized with pentobarbital (30 mg./kg.), administered intravenously. In the dogs in Group 1, three 10-minute control observations on renal clearances were made followed by three 10-minute periods taken during the continuous infusion of

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Aramine. The Aramine was given so as to increase blood pressure about 40 to 50 per cent above the control levels. However, this mark was exceeded in several instances. Renal plasma flow was measured by para-aminohippurate (PAH) clearance. Glomerular filtration rate was determined by creatinine clearance. Maximum tubular function was determined by the maximum reabsorptive capacity for glucose (TmG). Chemical methods and techniques have been previously described.[5] Arterial blood pressure was measured by direct arterial manometry (mercury). Sodium and potassium excretion rates were determined by a Beckman flame photometer.

TABLE IA. EFFECT OF ARMINE INFUSION ON BLOOD PRESSURE, GLOMERULAR FILTRATION RATE, AND RENAL PLASMA FLOW

DOG NO.	DOSE‡ (MG./MIN.)	MEAN BLOOD PRESSURE (MM. HG)			GLOMERULAR FILTRATION RATE (ML./MIN.)			RENAL PLASMA FLOW* (ML./MIN.)			FILTRATION FRACTION†		
		C	D_1	D_2	C	D_1	D_2	C	D_1	D_2	C	D_1	D_2
1.	0.125	148	204	189	28	25	14	154	118	55	.18	.21	.25
2.	0.130	135	184	182	26	18	10	118	75	39	.22	.24	.26
3.	0.050	146	192	186	24	32	22	83	96	68	.29	.33	.32
4.	0.020	113	153	155	44	42	49	175	165	185	.25	.25	.26
5.	0.100	126	215	205	49	49	30	190	176	90	.26	.28	.33
6.	0.100	152	253	246	50	30	9	204	109	25	.25	.28	.36
7.	1.000	134	203	233	41	4	1	170	13	3	.24	.31	.33
8.	0.120	124	225	215	43	32	31	170	103	99	.25	.31	.31
9.	0.100	126	223	208	36	42	41	163	148	155	.22	.28	.26
Mean	0.194	134	206x	202x	38	30	23#	159	111#	80x	.24	.28#	.30x
Per cent of control			154	151		79	61		70	50		117	125
Mean for per cent of control													
Norepinephrine (7 dogs)‡			149	—		57	—		48	—		134	—
Epinephrine (9 dogs)‡			143	—		47	—		38	—		122	—

C = Control observation, average of three consecutive 10-minute periods
D_1 = First 10-minute period after blood pressure elevation with intravenous infusion of Aramine
D_2 = Average of second and third 10-minute periods during continuous infusion of Aramine
* = Para-aminohippurate clearance
† = Filtration fraction = $\frac{\text{Glomerular filtration rate}}{\text{Renal plasma flow}}$
‡ = Continuous infusion
# = Statistically significant $p < 0.05$; x = statistically significant $p < 0.01$.

The techniques employed in the thirteen animals in Group 2 were essentially the same as those in Group 1. After suitable control periods, four of these dogs received Dibenzyline* (2 mg./kg.) and three received hexamethonium (5 mg./kg.) prior to administering the Aramine by continuous infusion as to Group 1. The

*N-phenoxyisopropyl-N-benzyl-β-chlorethylamine hydrochloride.

other six dogs were actually dogs from Group 1 which were given Dibenzyline one hour or more following an infusion of Aramine. Three more control periods (C_2) were collected in all of these animals just prior to administering the Dibenzyline. After adrenergic blockade was established two periods were collected and then the Aramine infusion was repeated (three successive 10-minute periods), the rate of infusion being at least three times that which was used prior to blockade. The blood pressure and renal hemodynamic responses to Aramine before (Tables IA and IB) and after adrenergic blockade (Tables IIIA and IIIB) were then compared.

TABLE IB. EFFECT OF ARAMINE INFUSION ON RENAL HEMODYNAMICS

DOG NO.	MEAN BLOOD PRESSURE (MM. HG)			HEMATOCRIT			RENAL BLOOD* FLOW (ML./MIN.)			RENAL VASCULAR RESISTANCE		
	C	D_1	D_2	C	D_1	D_2	C	D_1	D_2	C	D_1	D_2
1.	148	204	189	34	42	43	233	203	96	0.64	1.00	1.97
2.	135	184	182	41	43	43	200	132	68	0.68	1.39	2.68
3.	146	192	186	38	49	49	134	188	133	1.09	1.02	1.40
4.	113	153	155	31	36	36	254	258	289	0.44	0.59	0.54
5.	126	215	205	33	48	47	284	338	170	0.44	0.64	1.21
6.	152	253	246	41	65	65	346	311	71	0.44	0.81	3.46
7.	134	203	233	35	53	54	262	28	7	0.51	—	—
8.	124	225	215	33	49	49	254	202	194	0.49	1.11	1.11
9.	126	223	208	34	46	45	247	274	282	0.51	0.81	0.74
Mean	134	206[x]	202[x]	36	48[x]	48[x]	246	215	146#	0.58	0.92[x]	1.64[x]
Per cent of control		154	151		133	133		87	59		159	283
Mean for per cent of control												
Norepinephrine (7 dogs)		149	—		111	—		53	—		370	—
Epinephrine (9 dogs)		143	—		127	—		45	—		370	—

$$\text{Renal vascular resistance} = \frac{\text{Mean blood pressure}}{\text{Renal blood flow}}$$

$$\text{* = Renal blood flow} = \frac{\text{Renal plasma flow}}{\text{1-hematocrit}}$$

= Statistically significant $p < 0.05$; [x] = statistically significant $p < 0.01$.

See Table IA for key to abbreviations

RESULTS

The renal response to the continuous infusion of Aramine is seen in Tables IA and IB. As the blood pressure increased renal vasoconstriction occurred and renal blood flow was reduced. This was reflected in a very sharp increase in renal vascular resistance. When renal vasoconstriction became marked, the reduction in renal blood flow was associated with a depression in glomerular filtration rate. As the blood pressure remained elevated during successive hypertensive periods renal blood flow and glomerular filtration rate were frequently

TABLE II. EFFECT OF ARAMINE INFUSION ON WATER AND ELECTROLYTE EXCRETION

DOG NO.	URINE VOLUME (ML./MIN.)			EXCRETION IN URINE						PLASMA CONCENTRATION					
				SODIUM (μEq./MIN.)			POTASSIUM (μEq./MIN.)			SODIUM (mEq./L.)			POTASSIUM (mEq./L.)		
	C	D_1	D_2	C	D_1	D_2	C	D_1	D_2	C	D_1	D_2	C	D_1	D_2
1.	0.3	0.6	0.3	56	76	66	63	156	63	139	135	134	3.12	2.43	2.56
2.	0.3	0.4	0.4	13	13	16	17	3	4	136	137	134	3.53	3.07	3.53
3.	0.3	1.4	0.7	13	93	37	4	28	13	137	137	135	3.00	2.76	2.87
4.	0.6	1.0	1.2	11	23	23	14	14	18	144	144	144	3.40	3.28	3.05
5.	4.0	3.0	0.9	27	188	64	42	43	14	144	148	147	3.58	3.40	3.40
6.	1.0	0.9	0.5	40	73	43	31	6	3	144	144	144	3.33	3.35	3.35
7.	1.0	0.2	0.2	53	15	4	21	2	5	144	141	141	2.97	2.98	2.92
8.	6.4	2.9	3.0	54	140	110	48	23	16	140	144	144	3.05	2.69	2.70
9.	2.6	8.0	8.5	30	20	40	26	39	33	141	143	141	2.87	2.51	2.51
Mean	1.8	2.0	1.7	33	71*	45	30	35	19	141	141	140	3.21	2.94	2.99
Per cent of control		111	94		215	136		117	63		100	99		92	93

See Table IA for key to abbreviations.
* = Statistical significance — $p < 0.10$.

reduced further (Fig. 1) despite the fact that the blood pressure did not increase any more than during the previous hypertensive period. Although the filtration fraction increased, this was usually not marked.

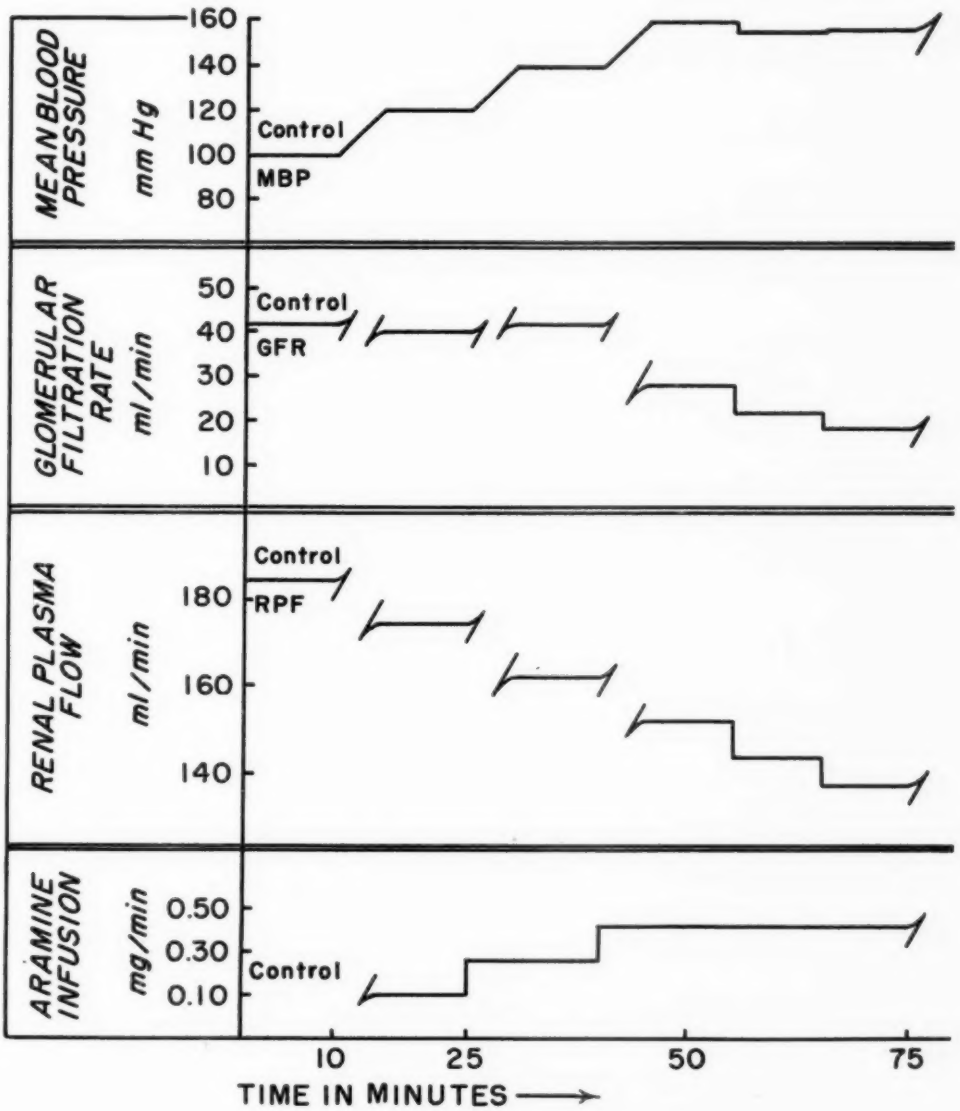

Fig. 1.—Typical renal hemodynamic response to a continuous infusion of Aramine in which the infusion was given in progressively larger amounts. As the blood pressure increased renal plasma flow was slightly depressed but glomerular filtration rate was not altered. With a more rapid infusion renal plasma flow was depressed further and glomerular filtration rate was also depressed. When the rate of infusion was rapid, renal function was progressively depressed despite the fact that the blood pressure did not increase above the previous hypertensive level.

TABLE IIIA. BLOOD PRESSURE AND RENAL CLEARANCES: EFFECT OF ADRENERGIC BLOCKADE ON THE RESPONSE TO ARAMINE INFUSION

DOG NO.	DOSE		MEAN BLOOD PRESSURE (MM./HG.)			GLOMERULAR FILTRATION RATE (ML./MIN.)			RENAL PLASMA* FLOW (ML./MIN.)			FILTRATION§ FRACTION			HEMATOCRIT			DOG WEIGHT
	DIBENZYLINE (MG./KG.)	ARAMINE‡ (MG./MIN.)	C_2	B_1	A_3	C_2	B_1	A_3	C_2	B_1	A_3	C_2	B_1	A_3	C_2	B_1	A_3	(KG.)
1.—D	5	0.120	128	104	97	45	41	40	216	183	166	.21	.22	.24	34	32	32	14.3
2.—D	5	0.500	166	94	93	47	41	40	174	220	209	.27	.19	.19	47	37	31	14.8
3.—D	5	0.560	181	97	97	41	44	42	161	165	134	.25	.27	.31	66	53	46	12.9
4.—D	5	2.000	113	73	78	15	24	29	75	90	110	.20	.27	.26	56	47	40	15.0
5.—D	5	0.800	147	88	89	34	28	26	133	156	139	.26	.18	.19	48	42	32	11.6
6.—D	5	0.660	147	86	79	43	27	27	188	161	190	.23	.17	.14	45	36	28	15.8
7.—D	5	1.125	147	64	61	27	27	24	98	153	165	.28	.18	.15	45	41	34	11.4
8.—D	5	0.750	157	105	85	26	28	23	90	121	113	.29	.23	.20	33	34	28	9.0
9.—D	5	0.600	155	73	65	22	31	27	81	121	139	.27	.26	.19	45	43	37	11.9
10.—D	5	0.600	151	69	69	34	26	22	101	123	108	.34	.21	.20	37	34	34	8.8
Mean	5	0.772	149	85[x]	81[x]	33	32	30	132	149	147	.26	.22#	.21#	46	40	34[x]	12.6
Per cent of control				57	54		97	91		113	111		85	81		87	74	

* = Para-aminohippurate clearance

§ = Filtration fraction = $\frac{\text{Glomerular filtration rate}}{\text{Renal plasma flow}}$

C_2 = Control observation, average of three consecutive 10-minute periods

B_1 = Observations after Dibenzyline (average of two 10-minute periods)

A_3 = Observations during Aramine infusion following adrenergic blockade with Dibenzyline (average of two 10-minute periods)

‡ = Continuous infusion of Aramine following adrenergic blockade with Dibenzyline

\# = Statistically significant $p < 0.05$; [x] = statistically significant $p < 0.01$.

TABLE IIIB. THE EFFECT OF ADRENERGIC BLOCKADE ON THE RENAL HEMODYNAMIC RESPONSE TO ARAMINE

DOG NO.	MEAN BLOOD PRESSURE (MM. HG)			RENAL BLOOD FLOW* (ML./MIN.)			RENAL VASCULAR RESISTANCE†			TmG			GFR‡/TmG		
	C_2	B_1	A_3	C_2	B_1	A_3	C_2	B_1	A_3	C_2	B_1	A_3	C_2	B_1	A_3
1.—D	128	104	97	327	269	244	.39	.39	.40	—	—	—	—	—	—
2.—D	166	94	93	328	349	303	.51	.27	.31	—	—	—	—	—	—
3.—D	181	97	97	474	351	248	.38	.28	.39	—	—	—	—	—	—
4.—D	113	73	78	170	170	183	.66	.43	.43	—	—	—	—	—	—
5.—D	147	88	89	256	269	204	.57	.33	.44	82	78	70	.41	.36	.37
6.—D	147	86	79	342	252	264	.43	.34	.30	117	97	106	.37	.28	.25
7.—D	147	64	61	178	259	250	.83	.25	.24	97	89	90	.28	.30	.27
8.—D	157	105	85	134	183	157	1.17	.57	.54	89	82	85	.29	.34	.27
9.—D	155	73	65	147	212	221	1.05	.34	.29	65	94	65	.34	.33	.42
10.—D	151	69	69	160	186	164	.94	.37	.42	106	92	66	.32	.28	.33
Mean	149	85[x]	81[x]	252	250	224	.69	.36[x]	.38[x]	93	89	80	.34	.32	.32
Per cent of control		57	54		99	89		52	55		96	86		94	94

TmG = Maximum tubular reabsorption of glucose in mg./min.

† = Renal vascular resistance = $\frac{\text{Mean blood pressure}}{\text{Renal blood flow}}$

* = Renal blood flow = $\frac{\text{Renal plasma flow}}{\text{1-hematocrit}}$

‡ = GFR = Glomerular filtration rate

C_2, B_1, and A_3—See Table IIIA for key to abbreviations

[x] = Statistically significant $p < 0.01$.

TABLE IV. ELECTROLYTE EXCRETION: EFFECT OF ADRENERGIC BLOCKADE ON THE RESPONSE TO ARAMINE INFUSION

DOG NO.	URINE VOLUME (ML./MIN.)			PLASMA CONCENTRATION						URINE EXCRETION					
				SODIUM (mEq./L.)			POTASSIUM (mEq./L.)			SODIUM (μEq./MIN.)			POTASSIUM (μEq./MIN.)		
	C_2	B_1	A_3	C_2	B_1	A_3	C_2	B_1	A_3	C_2	B_1	A_3	C_2	B_1	A_3
1.—D	1.8	1.2	1.2	144	144	144	3.0	2.4	2.3	22	19	38	19	16	23
2.—D	2.4	2.6	2.0	148	149	147	2.9	3.0	2.8	95	42	98	27	22	30
3.—D	0.9	0.6	0.5	141	144	140	2.9	2.3	2.4	35	32	29	17	16	12
4.—D	2.4	1.0	1.9	140	144	144	3.0	2.3	2.2	179	51	173	17	14	22
5.—D	7.6	5.9	7.2	144	144	144	2.9	2.8	2.1	566	298	438	33	33	37
6.—D	5.0	4.8	6.0	145	145	145	2.5	2.6	2.9	120	86	75	44	26	32
7.—D	0.8	2.4	6.4	133	139	122	3.1	2.5	2.6	7	58	73	7	9	18
8.—D	1.0	2.9	5.0	136	136	127	3.1	2.1	2.1	25	160	200	3	14	18
9.—D	0.7	2.4	4.8	136	135	133	3.6	2.4	3.3	12	79	107	1	10	20
10.—D	1.1	3.6	5.0	133	132	128	3.3	2.9	2.8	28	151	163	5	10	14
Mean	2.4	2.7	4.0	140	141	137	3.0	2.5[x]	2.6[#]	109	98	139	17	17	23
Per cent of control		113	167		101	98		83	87		90	128		100	135

See Table IIIA for key to abbreviations

[#] = Statistically significant — $p < 0.05$; [x] = statistically significant $p < 0.01$.

It is of interest that urine volume was not reduced except in several instances when glomerular filtration rate was markedly depressed. There was some increase in the average excretion of sodium but this was an inconstant response, the sharp increase in the mean value being due predominately to the response of a few dogs. At least there was no evidence of increased tubular reabsorption (decreased clearance) of sodium associated with the renal vasoconstriction produced by Aramine.

The renal hemodynamic response to Dibenzyline followed by Aramine infusion is presented in Tables IIIA and IIIB. Six of the dogs in this group are the same dogs presented in Tables IA and IB which received Aramine alone about one hour (rest period) or more prior to the Dibenzyline administration. The high blood pressures observed in some of the control studies in Table IIIA may be due to some residual effect of the previously administered Aramine. However, pentobarbital anesthesia also causes an elevation in the blood pressure. By comparing Tables IIIA and IIIB with IA and IB one can readily see the difference in response to Aramine when given after adrenergic blockade as compared to the response before blockade was established. When Dibenzyline was given it caused reduction in blood pressure. This was followed by renal vasodilatation and as a result renal blood flow was not altered. When Aramine was then infused the blood pressure was not altered appreciably despite the fact that (on the average) three times the amount of Aramine was used after Dibenzyline (Group 2) as was used in the animals (Group 1) which did not receive Dibenzyline (mean 0.194 mg./min. as compared to 0.772 mg./min., respectively). Blood pressure reversal as is seen after epinephrine and norepinephrine infusion was not observed after Aramine. The most significant observation was that Aramine did not produce renal vasoconstriction when administered following adrenergic blockade, as it did previously. This would appear to demonstrate renal adrenergic blockade at least of the vasoconstrictor receptors (probably adrenergic receptors) which respond to Aramine in the unblocked animal.

Dibenzyline did not appear to affect urine volume and about one-half of the animals showed a slight increase when Aramine was then administered. However, the increase in the mean value was due predominately to the response of only a few animals. The excretion of electrolytes did not appear to be altered consistently either by adrenergic blockade or by Aramine after adrenergic blockade.

Ganglionic blockade with hexamethonium did not alter the blood pressure response (qualitatively) produced by Aramine. However, since the blood pressure was first reduced with hexamethonium the percentile increase in blood pressure after Aramine was more marked since the base line after hexamethonium was at a lower level. In addition there seemed to be increased sensitivity to the vasopressor effect of Aramine much as is seen with norepinephrine, since the amount of drug infused was considerably less than that (0.018 mg./min.) required in a normal animal in order to produce an equivalent increase in blood pressure. As a result, the blood pressure rose with practically no alteration in renal blood flow or glomerular filtration rate. Aramine, when given after ganglionic blockade, appeared to increase both water and sodium excretion. This

may have been because greater elevations in blood pressure were obtained with less drug being infused and therefore less concurrent renal vasoconstriction. There was a slight increase in glomerular filtration rate (average of 4 c.c.) which would tend to support this concept.

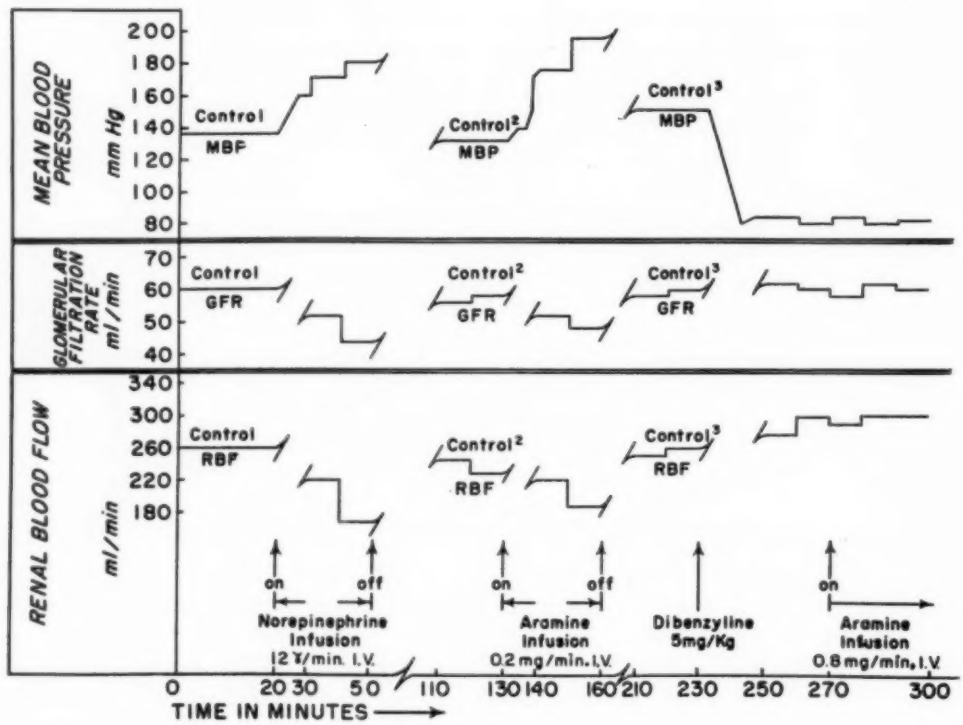

Fig. 2.—A norepinephrine infusion depresses both glomerular filtration rate (GFR) and renal blood flow (RBF) as the blood pressure rises. When norepinephrine is discontinued and Aramine is infused the reduction in renal function appears to be less than with norepinephrine for an equivalent increase in blood pressure. Following Dibenzyline the blood pressure falls but GFR and RBF are not altered. When Aramine is now infused, the blood pressure is not affected and RBF and GFR are not reduced due to adrenergic blockade of the kidney.

COMMENT

It appears that Aramine has the same effect on renal hemodynamics as norepinephrine. As the blood pressure increases, renal vascular resistance also increases. Renal blood flow is not altered at first but as vasoconstriction is more pronounced renal blood flow is reduced and later glomerular filtration is likewise depressed. However, it appears that with equal degrees of blood pressure elevation, the renal vasoconstrictive effect of Aramine is not as great as with norepinephrine (Tables IB and IIIB, Fig. 2).

When Dibenzyline is given before Aramine the blood pressure is not increased when Aramine is infused. The vasoconstrictive effect on the kidney is likewise completely blocked. This indicates that renal adrenergic blockade has been produced by Dibenzyline (or at least blockade of the vasoconstrictive

receptors which respond to Aramine in the normal animal). Presumably these receptors would be the same as those which respond to norepinephrine. However, when norepinephrine is infused the renal blocking effect cannot be so clearly demonstrated due to the sharp reduction in blood pressure (blood pressure reversal) which follows the infusion of norepinephrine and which itself depresses renal blood flow.

Aramine does not appear to produce a consistent effect on water and electrolyte excretion. If anything there is an increased clearance of these substances unless glomerular filtration rate is markedly reduced. Then the clearances of both sodium and water are depressed. This response is essentially the same response that Pullman and McClure[6] observed after the infusion of norepinephrine. However, Berne[4] has observed a reduction in sodium and water excretion in dogs which was not associated with a reduction in glomerular filtration rate. Presumably the reduction in sodium and water excretion under these circumstances would be due to increased tubular reabsorption of these substances. A similar divergence of opinion exists with reference to the effect of epinephrine on the renal excretion of water and sodium. Jacobson and his associates[7] observed a reduction in the urinary excretion in sodium and water which was closely related to a reduction in glomerular filtration rate. On the contrary Blake[8] and Kaplan and others[9] have observed a reduction in sodium excretion which was not related to glomerular filtration rate but was presumably on the basis of increased tubular reabsorption of this electrolyte.

It is our opinion that Aramine does not depress urinary excretion of sodium and water to the same degree that norepinephrine does because it appears to produce less renal vasoconstriction with similar degrees of systemic blood pressure elevations. Therefore, a depression of glomerular filtration rate is not an early response to Aramine infusion but only occurs following an excessive amount of the drug. This response has also been observed in human beings[10] to whom Aramine has been administered. It is quite likely that the differences of opinion among various investigators as to the effect of norepinephrine on water and electrolyte excretion are not real differences at all but rather are related to the amounts of norepinephrine and epinephrine employed. It has been our observation[11] that when relatively small amounts of norepinephrine and epinephrine are infused glomerular filtration rate is not depressed. At the same time sodium and water excretion are not altered or are actually increased. However, when the rate of norepinephrine or epinephrine infusion is increased so that glomerular filtration is depressed, then both sodium and water excretion are also depressed. There is no evidence in this study to indicate that adrenergic blockade of the renal nerves (with Dibenzyline) increases sodium and water excretion. This is in direct contrast to the reported effect of Hydergine (CCK-179) on the renal excretion of water and electrolytes.[12] Increased excretion of water and sodium follows the administration of this agent. The failure of Dibenzyline to produce a similar response, despite the demonstrated existence of renal adrenergic blockade, suggests that this response to Hydergine may be mediated through properties other than the adrenergic blockade which it produces.

SUMMARY AND CONCLUSIONS

1. Observations have been made on the acute renal hemodynamic response to a continuous intravenous infusion of Aramine. As the blood pressure increased renal vasoconstriction occurred and renal blood flow was depressed. When renal vasoconstriction became marked glomerular filtration was also depressed. The renal excretion of water and electrolytes was not altered in any consistent fashion unless glomerular filtration rate was markedly reduced. When this occurred the excretion rates of water and sodium were depressed.

2. The blood pressure and renal hemodynamic response to a continuous infusion of Aramine are completely blocked by the antecedent administration of Dibenzyline thus suggesting that the renal vasoconstrictive response to adrenergic drugs is blocked by adrenergic blockade.

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THE IMMEDIATE EFFECT OF CIGARETTES ON THE CIRCULATION OF HEALTHY AND HABITUAL MALE SMOKERS

A Study in Ballistocardiography

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ALTHOUGH the annual consumption of cigarettes in the United States is large, few recent studies deal with the effect of smoking on the heart and circulation. To advise patients who are habitual smokers regarding smoking, it is important to know what changes in the cardiac output, pulse, or skin temperatures (reflecting peripheral vasoconstriction), ballistic wave forms or arrhythmias, and circulatory changes may be produced in that individual by smoking. In an attempt to evaluate the effect of smoking on the heart and circulation, the ballistic wave pattern was obtained and cardiac output determined therefrom in normal subjects after smoking both their accustomed brand and commercial "low nicotine" brand cigarettes with the addition of a silica gel filter as a control. Simultaneous skin temperatures and pulse rates were recorded.

METHODS

Our subjects were fourteen convalescent male patients without cardiovascular disease from the Surgical Service of the Cincinnati General Hospital and three normal male volunteers, all of whom were habitual smokers whose ages ranged between 16 and 41 (average age 27.2). Each subject smoked two low nicotine cigarettes through a silica filter on the first day and one or two ordinary cigarettes with no filter on the subsequent day. Observations were made in the basal postabsorptive state following a rest period of at least 15 minutes. The pulse rate was determined from the electrocardiogram and the skin temperatures of the toes, fingers, and forehead were measured by the UMA clinical thermocouple. The ballistocardiogram was recorded on our high frequency research instrument[1] and the cardiac output was computed by the formula of Starr and associates.[2] All observations were made at intervals of three to five minutes and were submitted to statistical analysis.

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CRITIQUE OF METHOD

Because frequent observations of cardiac output were necessary during periods of one to two hours on consecutive days, it was felt that dye-injection techniques and oxygen studies with cardiac catheter were impractical for measuring cardiac output in this study. Criticism of the determination of cardiac output by ballistocardiogram has arisen, based largely on the work of Cournand and associates.[3] These authors studied cardiac output in a group of patients by the Fick method and almost simultaneous ballistocardiographic determinations. The Fick values were 18.5 per cent higher than the ballistocardiographic values. When correct values for aortic cross section were substituted in Starr's formula, the difference was only 3.5 per cent. Since then Tanner,[4] Molomut and Allen,[5] Scarborough and associates,[6] and Brown and associates[7] have found good reliability of the ballistocardiographic method in general, particularly when relative changes were observed in the same individual. Kaufman and associates[8] in this laboratory, in studies of the effect of drugs on cardiac output, found good correlation between the ballistocardiographic and other methods.

Recently Assali and associates[9] found good correlation between Fick and ballistocardiographic methods in our laboratory using the same ballistocardiographic table used in this study.

RESULTS

No change in the form of ballistocardiograms occurred after smoking either "low nicotine" (filter) or ordinary cigarettes.

Three of the subjects showed slight increases in cardiac output after smoking ordinary cigarettes and five subjects after smoking low nicotine cigarettes through a filter. One patient's cardiac output decreased slightly after ordinary cigarettes. The rest showed no change in output. None of these changes were statistically significant.

Statistical analysis comparing pre- and postsmoking outputs both with low nicotine (filtered) and ordinary cigarettes revealed no statistically significant differences. Low nicotine cigarettes: $t = 0.39$, $p = 0.7$; standard cigarettes: $t = 0.37$, $p = 0.7$. Therefore no significant change in cardiac output occurred after either test.

When the pulse rates were compared statistically in a similar manner before and after the smoking of both the low nicotine (filtered) and ordinary cigarettes, no significant difference was found with the low nicotine ($t = 1.84$, $p < 0.1$ but > 0.05) but a statistically significant increase in pulse rate occurred after the smoking of standard cigarettes ($t = 3.0$, $p < 0.01$).

In general the skin temperature changes in all our subjects followed the well-known pattern already previously described by Grollman,[10] Roth[11] and others, except in our subjects the temperature fall was not so pronounced in the lower extremities. When the skin temperature changes following smoking regular and low-nicotine cigarettes were compared, it was found that regular cigarettes produced significant decreases in temperature of forehead and fingers, but not of the toes (Table I).

TABLE I. STATISTICAL COMPARISON OF CHANGES IN SKIN TEMPERATURES PRODUCED BY SMOKING LOW NICOTINE (FILTERED) AND REGULAR CIGARETTES

SKIN AREA	*t*	*p*
Forehead	2.5	>0.01 but <0.02
Small toe (right)	1.05	>0.2 but <0.3
Large toe (right)	0.84	>0.4 but <0.5
Small toe (left)	0.45	>0.6 but <0.7
Large toe (left)	0.01	>0.9
Thumb (right)	2.93	<0.01
Small fingers (right)	3.39	<0.01
Thumb (left)	3.69	<0.01
Small fingers (left)	3.47	<0.01

<0.05 is significant.

Individual decreases in skin temperatures ranged from 1° to 14° F. reaching their maximum drop in the skin of the fingers.

DISCUSSION

Statistically significant changes in cardiac output following the smoking of ordinary cigarettes could not be demonstrated with the ballistocardiograph in spite of the fact that concurrent significant changes were found to occur in heart rates and skin temperatures. These latter changes are caused by nicotine (an alkaloid of tobacco) in producing both peripheral vasoconstriction and stimulation of the central nervous system.[11,12]

Various observers disagree on the incidence of ballistocardiographic changes following smoking. Dock and associates[13] found a high incidence of deterioration of the ballistic pattern in patients with angina pectoris or healed infarcts. Dock also mentions that in apparently normal individuals 10 per cent will show ballistocardiographic changes after smoking. Levy and associates,[15] studying the effects on the circulation of intravenous injection of nicotine using the ballistocardiogram, showed comparatively little effect on cardiac output and felt the changes described by Dock were explained on individual susceptibility or sensitivity to tobacco smoke. Starr and Hildreth[14] noted no difference between the records of smokers and nonsmokers.

Henderson[16] found in a very recent study in fifty normal young people that the form of the ballistocardiogram remained unchanged after smoking.

Individuals who show deterioration of the wave pattern or develop premature ventricular contractions or other arrhythmias, caused either by coronary atherosclerosis or individual susceptibility or both, should probably be advised not to smoke ordinary cigarettes. If changes persist, low nicotine filtered cigarettes could be tried. If still the changes persist, then we feel the patient should be advised to discontinue smoking, psychic factors being considered.

The evidence seems to indicate that while smoking will constrict peripheral vessels in normal young people, causing increase in heart rate and fall in skin temperature, the effect is not strong enough to change the form of the ballisto-

cardiogram or affect the cardiac output, except in cases of individual susceptibility or sensitivity. None of our subjects showed this latter effect.

CONCLUSION

1. In normal young men no significant change in cardiac output was found after smoking ordinary cigarettes.

2. While showing no change in cardiac output, these same normal young men showed concurrent statistically significant increases in pulse rates and decreases in skin temperatures.

3. In our patients there were no changes in the form of the ballistocardiogram following smoking.

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CARDIOSPECTROGRAMS

A Preliminary Report

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ONE of the principal advances in the electronic art within the last few years has been the improved technique of spectrum analysis. Basically, any phenomenon involving motion can be subjected to a wide variety of measuring and analyzing techniques. In certain cases a display of spectrum or spectrum analysis provides a greater insight into the nature and parameters of phenomena than any other single measurement. For this reason research workers in widely diversified fields have constantly striven to widen the possible application of spectrum-analysis techniques.

The present paper deals with one of these new applications, cardiospectrograms, in which a graphical-spectrum display is made of heart sounds. The significance of these records will be considered, and certain plans for future investigations suggested.

In general, spectrum analysis is a procedure whereby a measurement is made which considers the energy distribution of a physical occurrence as a function of time and frequency.

Much of the original interest in spectrum analysis has been directed toward speech research.[1] An entire science has evolved around this work resulting in improved radio and telephone communications apparatus and in devices for instruction of individuals with speech and hearing defects. More important, perhaps, a basic insight has been gained as to the mechanism of speech which had been for so long an elusive mystery.

A compilation of this work is available but a few highlights may be mentioned here to emphasize the significant features of the methods employed.[2] The sound spectrograph produces patterns that show the frequency components present in audible sounds. All of the various spectrograms reproduced in this report display frequency along the vertical axis, time along the horizontal axis, and intensity by the darkness of the pattern. Fig. 1 shows typical examples of certain of these speech sounds and it is readily seen that each vowel, consonant, and diphthong forms a distinct pattern. Furthermore, it has been possible to recognize the specific feature of a pattern and to determine what differentiates it from the pattern of any other sound.

During this same study it was possible to train individuals to identify spectrum patterns of complete words and sentences very rapidly. By use of a

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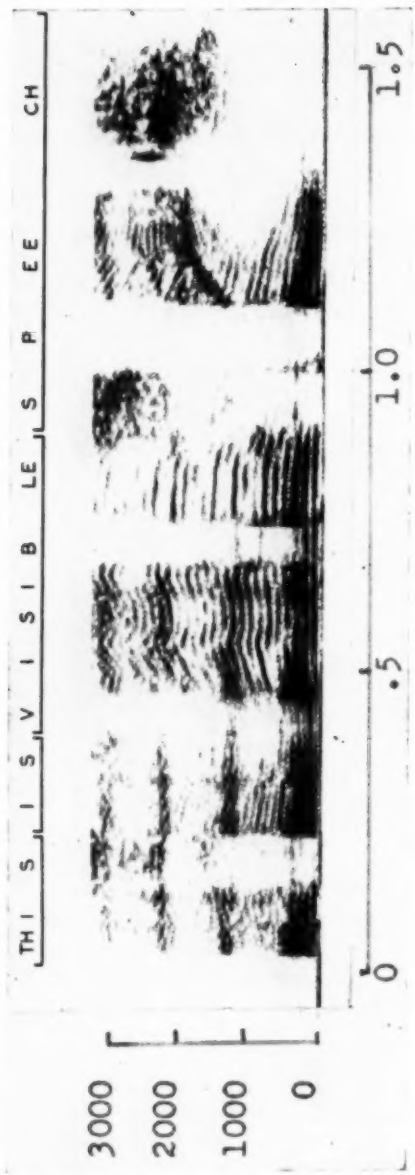

Fig. 1.—Spectrogram of speech sounds.

special sound spectrum device called a "Cathode-Ray Translator" two such highly trained individuals, using microphones in sound-proof rooms, were able to carry on normal conversation. Although neither could actually "hear" what the other was saying, the visible patterns of speech projected on the "Cathode-Ray Translator" enabled them to understand each other.

Although most of the initial applications of spectrum analysis have been for speech research, with the advent of improved magnetic-recording techniques many diverse fields have employed similar analysis procedures. Seismic exploration, shock and vibration studies, and noise analysis are but a few of the many investigations in which the date frequencies are first recorded on magnetic tape and then analyzed with spectrographic equipment. Very often, as in the case of heart sounds, low frequencies out of the range of hearing are very important for reproduction and study of certain phenomena. This results because inaudible sounds often are accompanied by overtones which are included in the sounds we hear. By playing back magnetic tape recording at a high-speed ratio, subaudible frequencies can be heard and more accurate spectrograms are made possible. For this type of work it is essential to use the finest possible equipment to insure the accurate reproduction and analysis of the original sounds. Included in earlier work are several spectrograms of heart sounds and murmurs by Potter and associates taken from phonograph records.[3] These do not come out clearly since they show the surface noise of the record material. This is reduced, of course, by magnetic tape recordings which also have the advantage of low-frequency reproduction.

The equipment used to record the heart sounds consisted of either a Brush contact microphone or a Western Electric 618A modified with a rubber seal, a low noise preamplifier, and an Ampex Model 300 magnetic tape recorder. The original heart-sound tape recordings were cut and spliced into continuous loops of approximately three and one-half seconds duration. The tape recordings were made at fifteen inches per second, increased in speed four times, and spectrograms made of them by courtesy of the Bell Telephone Laboratories. A photograph of typical equipment used by the Bell Telephone Laboratories for this purpose is shown in Fig. 2. To date we have made approximately 469 spectrograms of 110 hearts. Many of these have been made with different analysis techniques.

It has long been recognized that the frequencies of practically all heart sounds and murmurs are below 2,000 C.P.S. and that in the great majority the high end is never over 1,000 C.P.S.[4] The probability is that a physician using his stethoscope actually does not hear a great deal of the low-frequency end of the spectrum, and it may be that some hear things in the higher ranges that are not reproduced in these spectrograms which we have made. We intend to expand both the upper and lower ranges for further study.

Normal heart sounds at the apex have been described as having certain characteristics. While it must be agreed that in the majority of so-called normal individuals these sounds as heard with a stethoscope do conform to the description "the first sound is lower in pitch, louder and longer" than the second sound, an accurate visual portrayal of these sounds does not bear this out. In fact the wide variance of patterns of "normal" have stimulated us to try to determine just what does fall within that range. Fig. 3, a composite of ten normal patterns,

shows that the low component of the first sound (making it sound low pitched) predominates in some individuals but not in others; that the length of the sounds does not differ as much as one's audible experience leads one to think; and that a third sound is often seen when it cannot be heard. The matter of transmission of sounds also comes into the picture; in the thin individual the mitral second sound is often loud and sometimes louder than the first sound at the

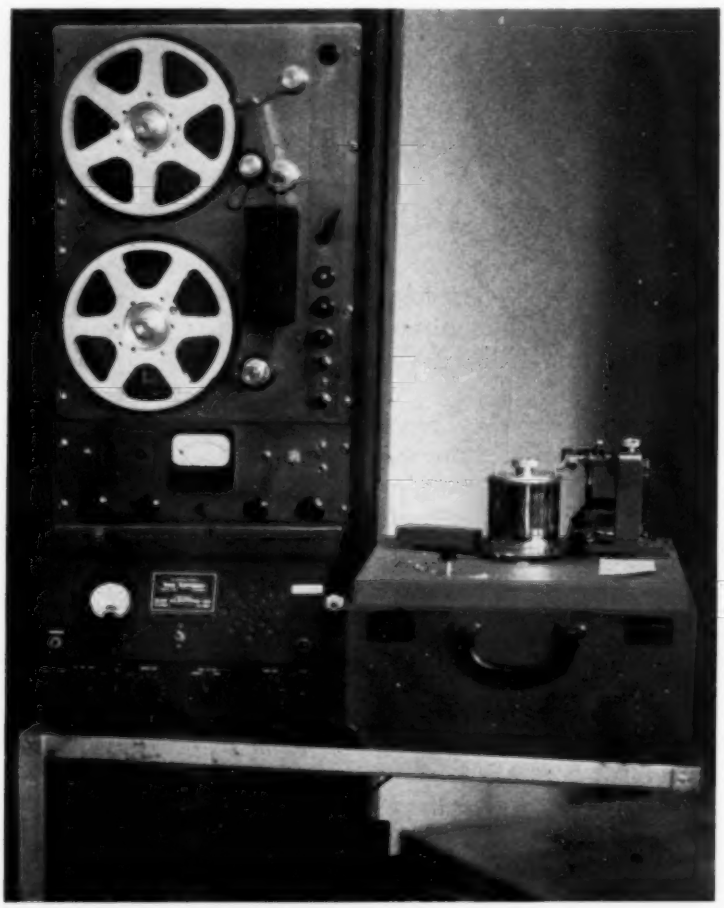

Fig. 2.—Apparatus used for cardiospectrograms.

apex. Whether this is due to the position of the heart in the chest, or to absence of dampening as the result of fat, or to transmission from other areas—the pulmonic in particular—with summation effect, needs further study.

The pattern of different murmurs becomes clearer as one learns to look for specific features, particularly pitch and time in the cardiac cycle. For a long time there has been discussion about whether the crescendo effect of presystolic murmurs is real or simply an auditory illusion. The visible answer of the wave frequencies seen on the spectrogram is that there is no increase in loudness of the murmur as it develops and that there is no increasing predominance of the low end which might make the murmur sound louder as it progresses up to the first

sound. The sharp element of the apical first sound associated with this murmur apparently is always short and high pitched, lacking a predominance of low frequencies, and it is these features which characterize it as "sharp." Its loudness or intensity is not a characteristic feature. This is well shown in Fig. 4. In this illustration there is also seen a second sound of considerable intensity, probably the result of transmission of that sound from the pulmonic area.

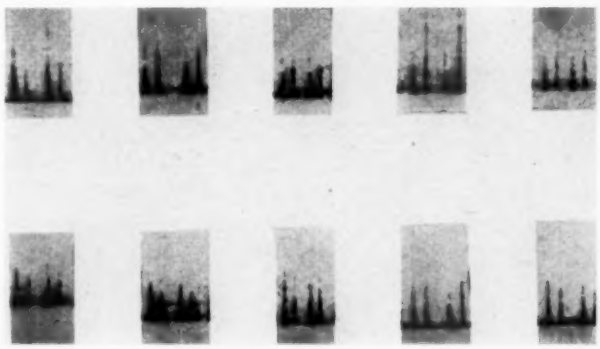

Fig. 3.—Composite of ten normal cardiospectrograms.

A rough systolic murmur in Fig. 5 shows the entire interval between the first and second sound occupied by this murmur whose pitch is recorded between 50 and 700 C.P.S. Fig. 6 shows a rough systolic murmur on which there is superimposed a musical element. This is well seen coming through at 900 to 1,000 C.P.S. It is interesting to see the different conformations of this element. The first cycle shows what looks like a capital A; this pattern changes during the next

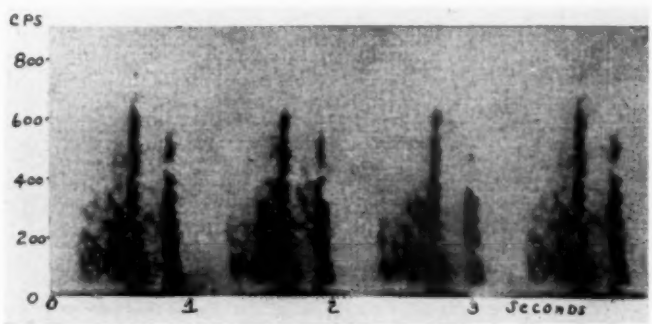

Fig. 4.—Sharp M_1.

two cycles but is then repeated in the fourth cycle. Respiratory effect caused this, the heart changing its position with respiration, the cardiorespiratory ratio being 72 to 18. Occasionally there is made a recording of an odd auscultatory finding. Two of these are seen on Fig. 7. From an auditory standpoint these sound like a grunt or the tuning of a base viol. There are seen two spectrograms of this phenomenon, one of which shows the abnormal sound in systole and the other in diastole. The first, taken at the second right intercostal space, was

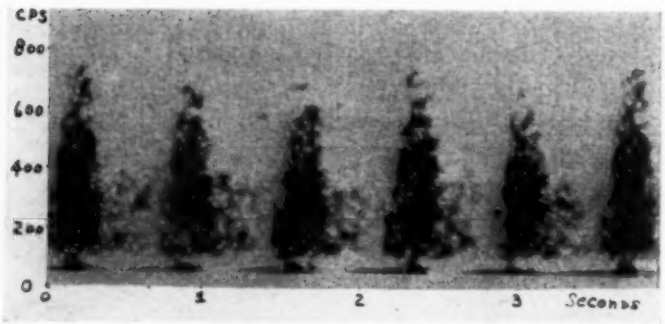

Fig. 5.—Rough systolic murmur.

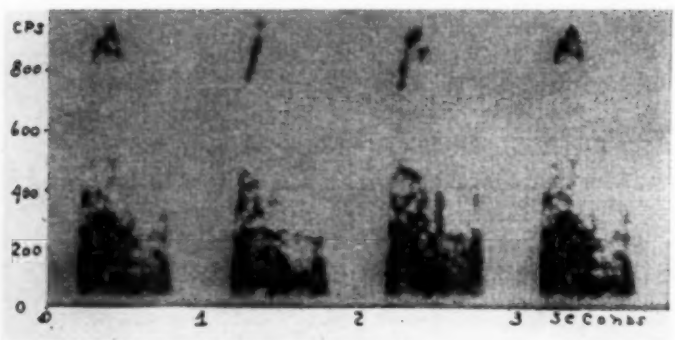

Fig. 6.—Rough musical systolic murmur.

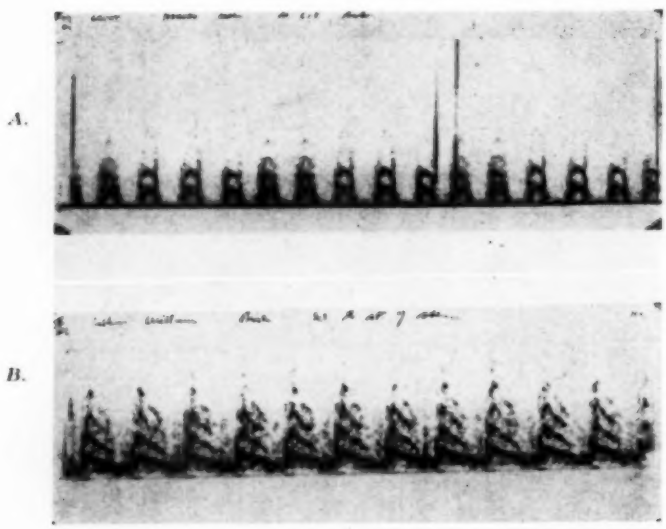

Fig. 7.—*A*, Systolic "grunt." *B*, Diastolic "grunt."

from a patient who had had a mitral commissurotomy. This was a transient phenomenon, gradually disappearing after about ten days and associated with no recognizable cardiovascular or other disturbance; it was felt it was not due to a pericarditis. His recovery was uneventful, and he has had a good result from

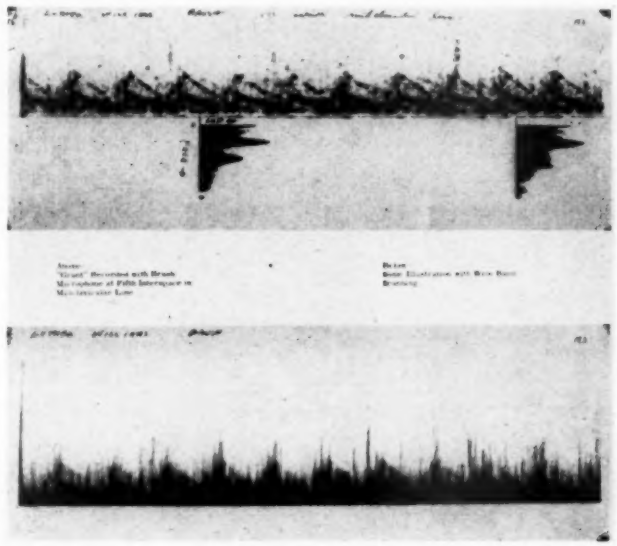

Fig. 8.—Diastolic "grunt" with intensity and wide band scanning.

surgery. The second, taken at the third right intercostal space, was from a patient with rheumatic aortic valvular disease, preponderantly aortic insufficiency. Fig. 8 shows the record of this same patient with a different microphone used at the apex. At a given point there is projected the intensity of the component bands of the spectrum and in the lower frame the same case with wide band scanning.

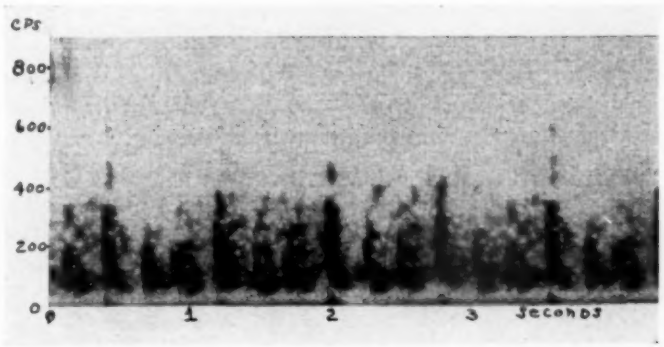

Fig. 9.—Gallop rhythm.

So far as we have gone, the patterns consisting of three sounds are quite distinct. Gallop rhythm consists of three sounds which are shown in Fig. 9. It is easily distinguished from the opening snap of mitral stenosis (a widely reduplicated mitral second sound) as seen in Fig. 10 and a systolic click seen in

Fig. 11. The spacing of this third sound in both of these illustrations is interesting and may prove to be significant.

Further work is in progress to perfect technique, and we believe that much clearer, cleaner patterns will result. We hope in the near future to have a chart which will show all types of normal and abnormal auscultatory findings. It is also possible to produce color spectrograms from sounds and the possible application of this method is being investigated.

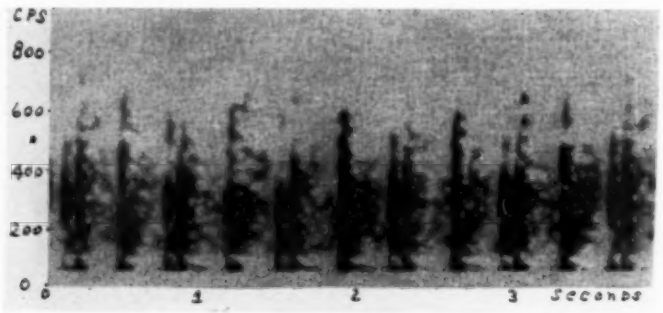

Fig. 10.—Opening snap.

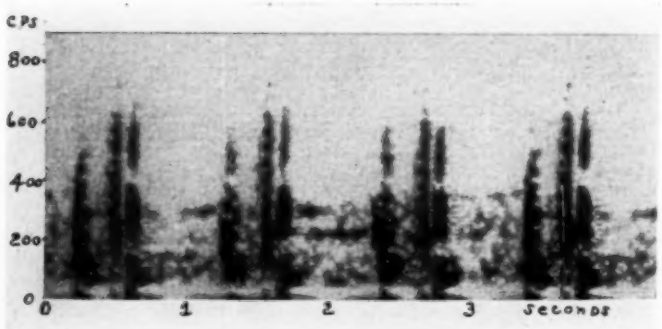

Fig. 11.—Systolic click.

It is difficult to predetermine the value of the application of this new method. In addition to clarifying certain features of normal and abnormal sounds and murmurs, it may be that it will prove a valuable aid in teaching auscultatory diagnosis. However, we are satisfied from previous investigation that it would be a mistake to try to simultaneously hear and "see" heart sounds and murmurs, for instead of emphasizing and clarifying this tends to confuse because of the difference in auditory and visual stimuli-reaction times. In addition to bringing to the surface new information it may develop into a new tool for clinical use or prove of value in screening programs.

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LEFT VENTRICULAR PRESSURE MEASUREMENT IN MAN

A New Method

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ANALYSIS of pressure curves from the different chambers of the heart is helpful in the diagnosis of multivalvular disease. The right side of the heart is easily accessible by ordinary heart catheterization and the left side of the heart is occasionally entered when a catheter from the right side passes through a septal defect or an open foramen ovale.

The left atrium was first punctured for pressure measurements through a bronchoscope by Lemoin in 1952.[1] A method of direct paravertebral puncture of the left atrium in man has now been used in 60 patients[2-4] in the Sabbatsberg Hospital.

The left ventricle was catheterized from the ulnar artery in 1948 by Zimmerman and associates[5,6] and in order to avoid damaging the aortic valve leaflets, patients with functional and organic insufficiency of the aortic valve were selected. Steinberg and associates[7] proposed that the catheter be made to form a loop with its blunt end entering the chamber of the left ventricle first. Retrograde catheterization in a patient with aortic stenosis would probably be difficult and the blind introduction of a needle directly through the left ventricular wall[8] is too dangerous as a diagnostic procedure because a coronary artery may be injured or ventricular fibrillation induced.

In the method reported here a needle is first introduced into the left atrium[2-4] and a small plastic catheter[9] is then threaded through the needle via the left atrium into the left ventricle.

TECHNIQUE

After previous x-ray localization of the left atrium the patient is placed on his left side and a skin wheal is made with ½ per cent procaine without Adrenalin over the ninth rib, about 5 cm. to the right of the spinous process.

A 20 cm. needle with 1½ mm. outside diameter and 1 mm. inside diameter (manufactured by Stille, Sweden) is introduced along the upper border of the

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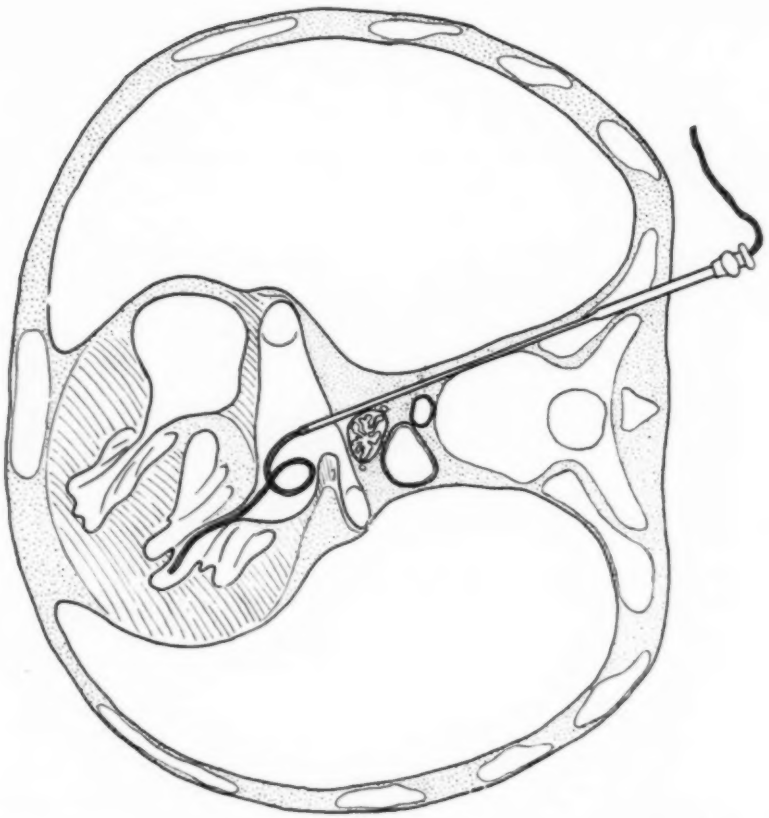

Fig. 1.—Cross sectional diagram showing a small plastic catheter introduced into the left ventricle through a needle placed in the left atrium.

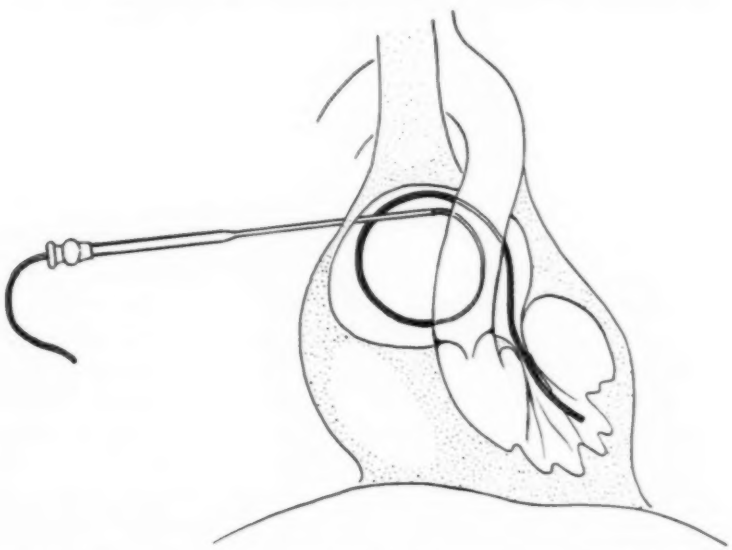

Fig. 2.—Sagittal plane diagram with the plastic catheter in the left ventricle.

right ninth rib to the vertebral body. The needle is then reinserted along the border of the vertebra until it enters the left atrium at which time bright red blood is aspirated. The correct position of the needle is determined by comparison of the oxygen tension in blood samples simultaneously obtained from the brachial artery and the left atrium. The oxygen tension of blood from the left atrium is uniformly several millimeters higher than the oxygen tension of blood from the brachial artery.[4]

A characteristic pressure curve from the left atrium confirms the position of the needle. (The Warburg and Hansen capacitance manometer has been used and the tracings are recorded with an Elema 6-channel "Clinic Apparatus").

A small plastic catheter is then introduced through the needle into the left atrium and manipulated through the mitral valves into the left ventricle (Figs. 1 and 2). The position of the catheter is immediately confirmed by the change in the pressure curve[10] (Figs. 5 and 6). Simultaneous pressure measurements in the left and right ventricle may also be recorded (Fig. 8).

CASE REPORT

A 31-year-old man had rheumatic fever in 1935 and 1940. In 1953, he noticed dyspnea on exertion and had hemoptysis. His heart volume was 1,020 ml. (530 ml. per square body surface). On x-ray there was a considerable enlargement of the left atrium and some enlargement of the left ventricle. There was a presystolic and a diastolic murmur over the apex as well as a systolic murmur to the left of the sternum in the third intercostal space. The second pulmonary sound was accentuated and his blood pressure was 130/95 mm. Hg. Electrokymography showed signs of mitral stenosis without regurgitation and an electrocardiogram showed sinus rhythm. His working capacity was 750 kilogram meters per minute. Pressures obtained by direct puncture of the left atrium with catheterization of the left ventricle are shown in Table I and the same systolic pressure was recorded from the left ventricle and the brachial artery (Fig. 7). The configuration of the left atrial curve is typical for a mitral stenosis without regurgitation (Fig. 4). At operation a pure mitral stenosis without regurgitation was found.

TABLE I. SIMULTANEOUS PRESSURE MEASUREMENTS IN LEFT VENTRICLE AND BRACHIAL ARTERY IN MITRAL STENOSIS; SIMULTANEOUS CATHETERIZATION OF LEFT AND RIGHT SIDE OF HEART

	PRESSURES IN MM. HG		
	MEAN	SYSTOLIC	DIASTOLIC
Left ventricle	66	164	5
Brachial artery	120	161	87
Left atrium	7.3	13.6	
Pulmonary capillaries	10		
Pulmonary artery at rest	25	38	17
Pulmonary artery during exercise	35	43	27
Right ventricle	10	34	0
Right atrium	−1		

The puncture of the left atrium may be somewhat more difficult in patients whose left atrium is of normal size. If there is a small left auricle, the lung is more easily injured and a pneumothorax may occur. Therefore, an x-ray of the chest is always taken after the investigation to determine if an aspiration of the pneumothorax may be necessary. This technique of left ventricular

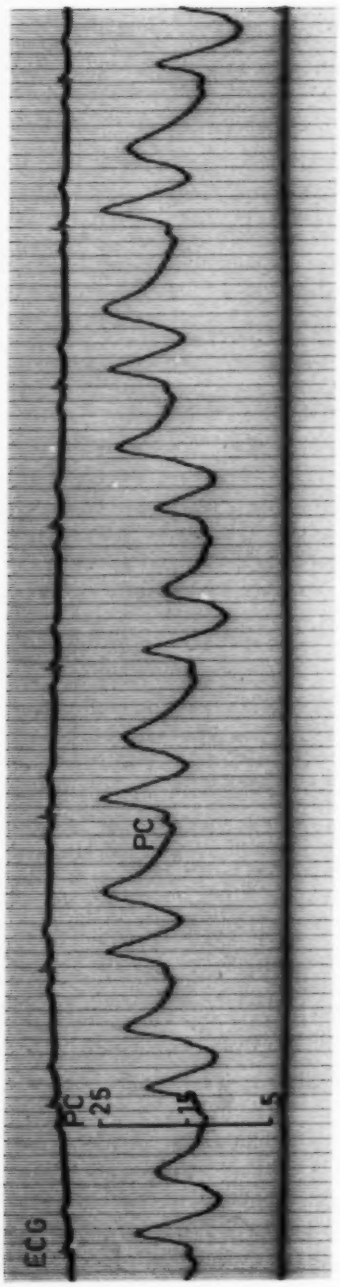

Fig. 3.—*PC*, Pulmonary capillary pressure curve.

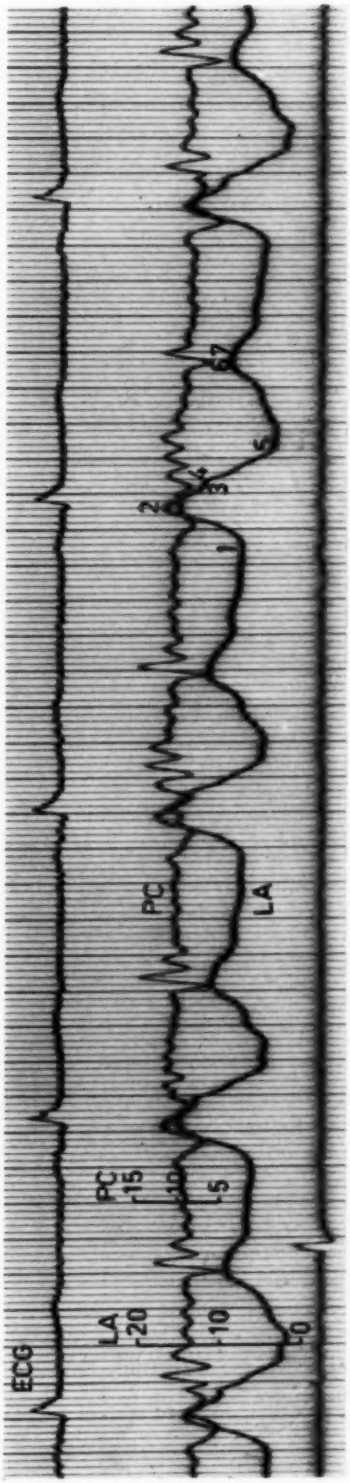

Fig. 4.—*LA*, Left atrial pressure curve obtained through the needle. *1-2-3*, Atrial systole. *4*, Closure of the mitral valves. *4-5*, Descent of the ventricular base. *6*, Closure of the aortic valves at the beginning of the second heart sound. *7*, Opening of the mitral valves.

catheterization has been attempted and successfully performed in 28 cases, and it seems advisable that this procedure be carried out by or in close collaboration with a thoracic surgeon.

When the catheter is withdrawn the needle should be removed first and then the catheter. If the catheter is withdrawn with the needle in place, a kink of the catheter may make it difficult to remove the catheter and dangerous to force it through the sharp opening of the needle.

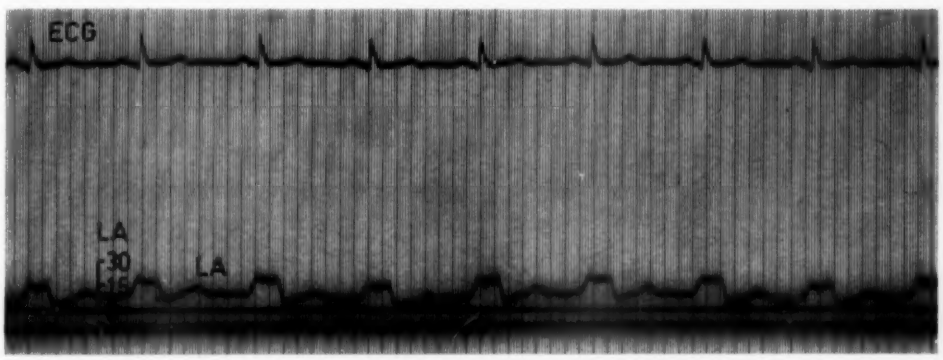

Fig. 5.—*LA*, The left atrial pressure curve obtained through the small plastic catheter which has been introduced through the needle.

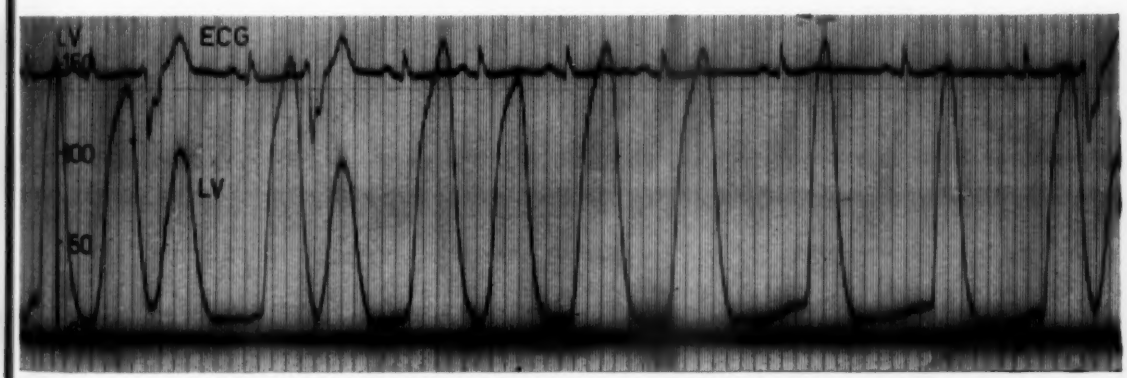

Fig. 6.—*LV*, The left ventricular curve obtained after manipulating the small plastic catheter from the left atrium into the ventricle.

Previous experience in dogs with this type of catheter would indicate that it is dangerous to try to manipulate the catheter into the aorta from the ventricle.[11] Schnabel and his associates using this size and larger and stiffer catheters have reported endocardial lesions, and in one instance a catheter tied itself around one of the chordae tendineae in the right ventricle of a dog.

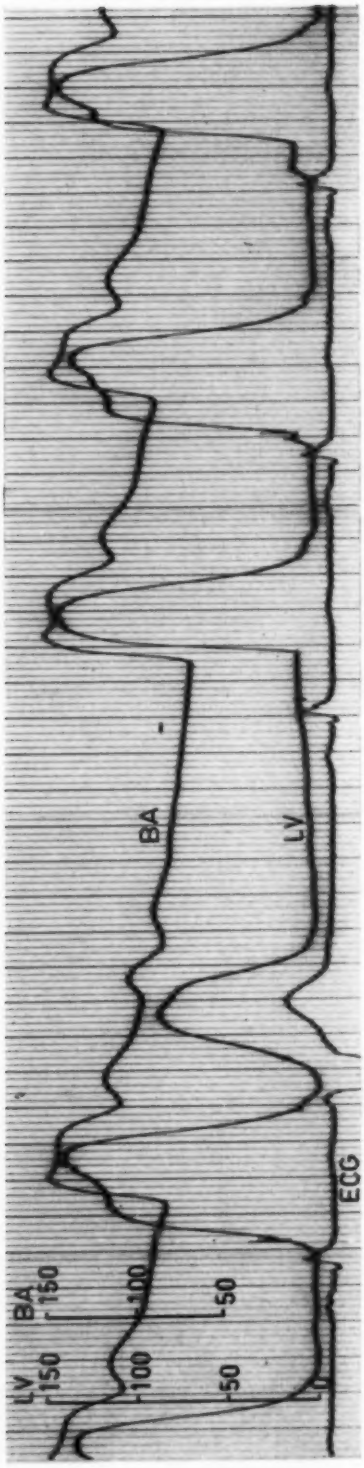

Fig. 7.—Simultaneous pressure measurements in the left ventricle (*LV*) and the brachial artery (*BA*) showing the same level of systolic pressure (Table I).

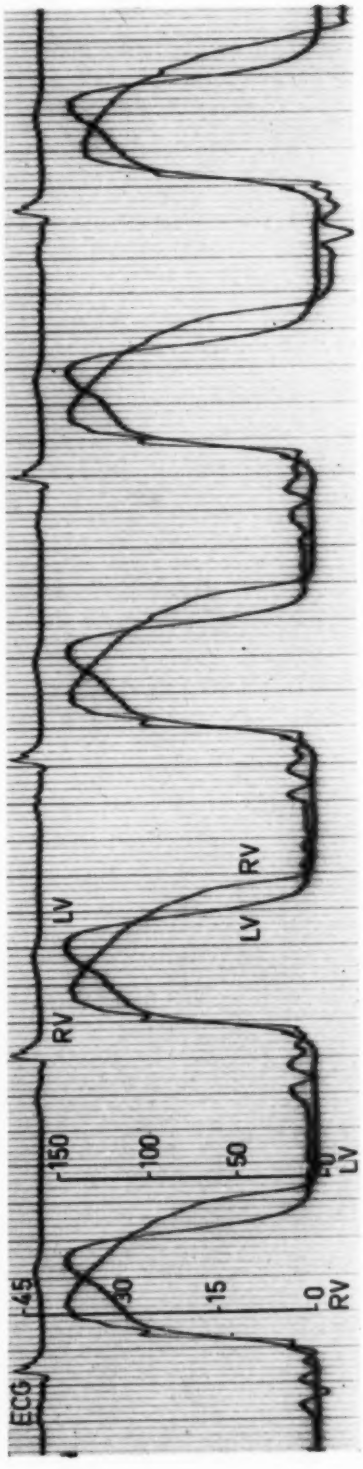

Fig. 8.—Simultaneous pressure measurements in the left (*LV*) and right ventricle (*RV*).

SUMMARY

A new technique is described for measuring the left ventricular pressure curve in the unanesthetized man. The method may be helpful in patients with aortic valvular disease with or without diseased mitral valves.

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UNIPOLAR VALUE OF STANDARD LIMB LEADS: LEAD -VR AND RATIONAL ARRANGEMENT OF LIMB LEADS

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THE introduction in electrocardiography of unipolar limb leads seems to have undervalued the meaning and the importance of Einthoven's standard bipolar leads. This is, at least, the opinion of many authors and generally of those who study electrocardiography with practical or scientific purposes. It would be difficult to present a complete bibliography on this subject, because it would include almost all the works on the argument of the last 15 years. We shall only mention a statement by Myers and Klein,[1] which condenses very well the current opinion: "If unipolar limb leads and multiple precordial leads are available, standard limb leads are superfluous. They contribute no information that cannot be derived more precisely from the unipolar limb leads studied in conjunction with multiple precordial leads. The main reason for continuance in this laboratory is for comparative purposes in return cases in which the standard leads were the only available limb leads."

The cause of this undervaluation is the belief that only "unipolar" leads are able to give a faithful picture of the potential variations occurring in the myocardium, and precisely in that part of the myocardium facing the exploring electrode, since the indifferent electrode has no influence on the tracing, or a negligible one; while bipolar leads would only allow the registration of "mixed" curves (resulting from the composition of potentials collected by both electrodes and therefore from different myocardial regions) and thus would require, in order to obtain a correct interpretation, an analysis based on the single components (the unipolar limb leads). That is why bipolar limb leads are kept quite separated from unipolar limb leads and are taken into little or no consideration, especially in the morphologic comparisons with the unipolar precordial leads.

This view is misleading, being based only on arbitrary, theoretical assumptions, and it is surprising that it is still considered valid in spite of actual opposite demonstration. There are in fact authors[2,3] who, on the basis of theoretical and experimental observations, denied any superiority of unipolar over bipolar limb leads (sometimes falling into the opposite mistake of considering the latter more important than the former). We have stated in the past[4,5] that standard and unipolar limb leads have an identical meaning. They must be interpreted with identical criteria and there is no question of superiority between the two groups.

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The aim of this paper is to prove: (1) that we can apply the unipolar interpretation to the standard limb leads exactly as to the unipolar limb leads and independently from the latter; (2) that Lead VR (or aVR) must be replaced by Lead –VR (or –aVR); and (3) that the present set of the limb leads must be replaced by a more rational one in which standard and unipolar limb leads must not be kept separated but disposed in alternate succession.

THEORETICAL CONSIDERATIONS

A "unipolar" lead has, in the strict sense, no meaning. Every lead records the potential differences between two points, no matter how these may be connected with the generator of the electromotive forces. In electrocardiography the term "unipolar" means a lead whose result is influenced by the potentials collected by only one electrode (exploring electrode), while the other one (indifferent electrode) is constantly at zero potential. The meaning of the word "unipolar" is, therefore, conventional. Moreover, these characteristics are never completely realized, as several researches have already shown; consequently, the so-called unipolar leads are actually bipolar leads (for this reason some authors[6] prefer to call them "V leads" or "aV leads"). Nevertheless, the potentials collected by the indifferent electrode are so small that they can practically be neglected by using the central-terminal of Wilson and co-workers.[7,8] But there are other leads which are regarded as unipolar leads, though their registration method does not correspond to the above mentioned requirements. They are Goldberger's[9] "augmented" unipolar limb leads which are quite bipolar. Some inaccuracies of such leads can be avoided through arrangements[10,11] which do not alter the bipolar character of the registration.

The possibility of recording, by means of bipolar leads, patterns whose shape is identical to the one obtainable with unipolar leads has been implicitly stated by Wilson[12]: "If the cardiac field at points far distant from the heart is nearly equivalent to that of a doublet, leads from two points equidistant from this organ and at opposite ends of a line which passes through its center should yield complexes exactly opposite in character if the leads employed are unipolar." If, therefore, a bipolar lead should be registered from these two points the resulting pattern would be exactly of the same shape (and double in voltage) of the unipolar-recorded tracing from one of these two points. This fact has already experimentally been proved by Selvini[13] on an isolated frog's heart. These leads, of course, (as well as the aV leads) cannot be termed unipolar. Yet their tracings are exactly of the same aspect as those obtained with unipolar leads registered from convenient points of the cardiac electric field. In this sense they could be considered "equivalent" to unipolar leads.

Within these limits it is possible to affirm that any kind of bipolar lead, at least when the electrodes are placed at a sufficient distance from the cardiac surface (2 to 3 cm. according to Gillmann,[14] any point of the body surface according to Bohning and co-workers,[15]) has a corresponding "equivalent" unipolar lead even if the two electrodes are not placed at the opposite ends of the same axis passing through the center of the cardiac electric field and if the two electrodes are at different distances from this center (see Appendix). The frontal

vectorcardiogram is a vectorial synthesis both of the unipolar and of the standard limb leads (Duchosal and associates,[16,17] Donzelot and Milovanovich,[18] Minot,[19] Routier[20]). Starting from the vectorcardiogram in the frontal plane we can deduce with a uniform procedure the standard as well as the unipolar limb leads. This well-known fact is essential; it proves indeed that no substantial difference exists between these two groups of leads. The shape of each limb lead depends only on the orientation of its directional axis in reference to the vectorcardiogram, independently from the unipolarity or bipolarity of the lead.

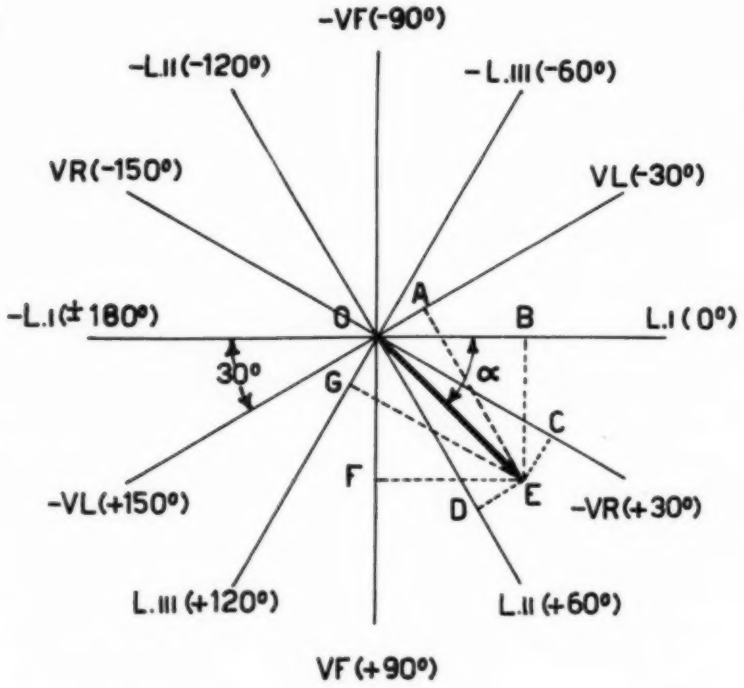

Fig. 1.—Hexaxial diagram in the frontal plane. Discussed in the text.

The relationship between these leads can be better analyzed considering Fig. 1. It represents an hexaxial diagram, that is a triaxial diagram of Bayley[21] (formed by the axes of the standard limb leads) to which three axes corresponding to unipolar limb leads have been added (Sodi-Pallares and co-workers[22]). *E* is one of the vectors belonging to the vectorial ring of the frontal plane. What will be said about *E* can be applied to all other vectors of the frontal plane. If we record unipolar leads from the points −150°, −30°, 0°, +60°, +90° and +120° the result will be proportional, in each one, to the projection of *E* on the relative lead axis. Since the distances of the lead points from the center of the electric field *O* are equal we may simply admit that the effect of *E* on every single lead is equal to its respective projections on each single axis, that is: $V_{-150°} = -OC$; $V_{-30°} = OA$; $V_{0°} = OB$; $V_{+160°} = OD$; $V_{+90°} = OF$; $V_{+120°} = OG$.

The effect of the vector E on a bipolar lead recorded from the points $-30°$ and $-150°$ can be established, according to Hill[23] and others, as follows: $V_{-30°} - V_{-150°} = V_{0°} \cdot \sqrt{3}$.* But $V_{-30°} = VL$, and $V_{-150°} = VR$, then Lead I $= V_{0°} \cdot \sqrt{3}$. Likewise, it can be demonstrated that Lead II $= V_{+60°} \cdot \sqrt{3}$ and Lead III $= V_{+120°} \cdot \sqrt{3}$. Standard limb leads give, therefore, the same result as particularly augmented unipolar leads registered from the ends $0°$, $+60°$ and $+120°$ of the respective lead axes; the "augmentation" ratio is of $\sqrt{3} : 1$ (that is 1.7:1). It should also be remembered that Goldberger's augmented unipolar limb leads give the following results: $aVR = V_{-150°} \cdot 3/2$; $aVL = V_{-30°} \cdot 3/2$; $aVF = V_{+90°} \cdot 3/2$ and that Wilson's unipolar limb leads are usually recorded with a standardization double the normal, that is 1 mv. = 2 cm. We can, therefore, state that all limb leads (including standard limb leads) can be considered "equivalent" to unipolar leads whose ratio of "augmentation" changes according to the method of registration. The ratio of such augmentation is the following:

aV limb leads (Goldberger)	= (Projection of E) .	1.5
Standard limb leads (Einthoven)	= (Projection of E) .	1.7
V limb leads (Wilson; 1 mv. = 2 cm.)	= (Projection of E) .	2.0

It is possible to remove any difference in the rate of augmentation of these leads by changing the standardization. If standard limb leads are registered with a calibration of 1 mv. = 1 cm., aV leads should be registered with a calibration of 1 mv. = 1.13 cm.; and V leads with a calibration of 1 mv. = 1.73 cm. This correction (which can be overlooked for practical purposes, but which must be taken in account in experimental analysis) does not alter in any way the shape and chronology of the tracings but only their size.

What we have said on the equivalence between unipolar and bipolar limb leads is reversible. In fact it is possible to prove that unipolar limb leads give the same results as bipolar leads registered in the frontal plane. This is true not only for aV leads (which do not need such a demonstration, being actually registered as bipolar leads) but also for V leads.† These observations prove

*The demonstration is the following:
$V_{-30°} - V_{-150°} = OA - (-OC) = OA + OC$, but $OA = E. \cos(\alpha + 30°)$ and $OC = E. \cos(\alpha - 30°)$ then:
$V_{-30°} - V_{-150°} = E. \cos(\alpha + 30°) + E. \cos(\alpha - 30°) = E. \cos \alpha \cdot \sqrt{3}$ and because $E. \cos \alpha = OB = V_{0°}$ it will be:
$V_{-30°} - V_{-150°} = V_{0°} \cdot \sqrt{3}$ Likewise it is demonstrated that:
$V_{+90°} - V_{-150°} = V_{+60°} \cdot \sqrt{3}$
$V_{+90°} - V_{-30°} = V_{+120°} \cdot \sqrt{3}$

†In fact if we register a bipolar lead from the points $0°$ and $+120°$ (Fig. 1) we obtain the following result:
$V_{0°} - V_{+120°} = OB - OG = E. \cos \alpha - E. \cos(120° - \alpha) = \sqrt{3}. E. \cos(\alpha + 30°)$
but $E. \cos(\alpha + 30°) = OA = V_{-30°} = VL$ then

$$V_{0°} - V_{+120°} = VL \cdot \sqrt{3} \quad \text{from which} \quad VL = \frac{V_{0°} - V_{+120°}}{\sqrt{3}}.$$

The VL unipolar lead, therefore, can be obtained by a bipolar lead from the points $0°$ and $+120°$. Likewise, it is demonstrated that:

$$VR = \frac{V_{-120°} - V_{0°}}{\sqrt{3}} \quad \text{and} \quad VF = \frac{V_{+120°} - V_{-120°}}{\sqrt{3}}.$$

that, in theory, there is no substantial difference between unipolar and standard limb leads and that, in spite of different registration methods, they can all be considered equivalent to unipolar (or bipolar) leads in the frontal plane, since all of them give tracings which could be obtained by current "unipolar" (or "bipolar") methods. We shall see that this statement is proved also experimentally.

It is here obvious to remark that the present arrangement of limb leads in two separate groups (Lead I, Lead II, Lead III and VR, VL, VF) is not only arbitrary, but also at random. Such arrangement corresponds to the registration of six leads recorded successively from the following points (Fig. 1): 0° (Lead I); +60° (Lead II); +120° (Lead III); −150° (VR); −30° (VL); +90° (VF). It would be more rational to dispose the leads according to their actual succession in the frontal plane so that, starting from one of them (e.g., VR or better VL) one could meet all the others in right succession: −30° (VL); 0° (Lead I); +60° (Lead II); +90° (VF); +120° (Lead III); −150° (VR). Then we can point out that while the intervals between VL and Lead I, Lead II and VF, VF and Lead III, are of 30°, the interval between Lead I and Lead II is of 60° and between Lead III and VR is of 90°. These discrepancies can easily be eliminated replacing Lead VR (−150°) with Lead −VR (−30°) registered from the opposite end of the directional axis of VR (Fig. 1) and equal to the mirror image of Lead VR. The pattern of the leads in the frontal plane becomes the following: VL(−30°); Lead I(0°); −VR(+30°); Lead II(+60°); VF(+90°); Lead III(+120°) and the intervals among the various leads become regular. This is the only rational arrangement of the limb leads. It allows a proper exploration of the frontal plane along a semicircle which embraces the apex of the heart and through unipolar (or equivalent to unipolar) leads at regular intervals of 30°. Moreover, it allows a reading of the peripheral electrocardiogram closely similar to the one of the precordial electrocardiogram which consists also of six unipolar leads placed on an arc embracing the apex of the heart at fairly regular intervals.

EXPERIMENTAL CONTROLS

Four experimental controls of the theoretical assumptions discussed here were performed.

First Control.—Standard limb leads and augmented unipolar limb leads (Goldberger) were registered in two subjects. Afterwards the same leads were registered with inverted polarity in order to obtain their mirror images. These twelve tracings were placed at the ends of an hexaxial diagram, the usual tracings at the positive ends and the specular ones at the negative ends (Figs. 2 and 3). We can observe: (a) Starting from aVL and proceeding clockwise the aspect of both auricular and ventricular complexes changes gradually from each lead to the next one; (b) Lead −aVR is properly inserted between Lead I and Lead II and forms, from the morphologic point of view, a bridge between these two standard leads; (c) Fig. 3 shows the record of a patient with bigeminous ventricular premature beats; note the intermediate aspect of lead −aVR between Lead I and Lead II and the gradual morphologic change from each lead into the next one, as well in the sinusal as in the ventricular extrasystolic beat.

Then, from the morphologic point of view, standard limb leads do insert suitably among unipolar limb leads (and reciprocally). No difference can be discovered among these leads except the one depending upon the different orientation in the frontal plane. A whole exploration of the frontal plane needs only six limb leads. Mirror images can be neglected since they give no supplementary information. Between Lead aVL and Lead III, five of the six traditional leads are

included. By replacing Lead aVR with Lead −aVR it is possible to complete the arc of the circle, to regularize the intervals between one lead and another, and to ensure that all limb leads may be registered from the same side of the frontal plane; and likewise to reproduce what takes place in the horizontal plane with the precordial unipolar leads. Besides, Lead −aVR, showing an intermediate aspect between that of Lead I and Lead II, can be directly compared with all other usual leads, arousing a greater interest than the original Lead aVR. Fig. 4 shows some examples of rational arrangement from Lead aVL to Lead III.

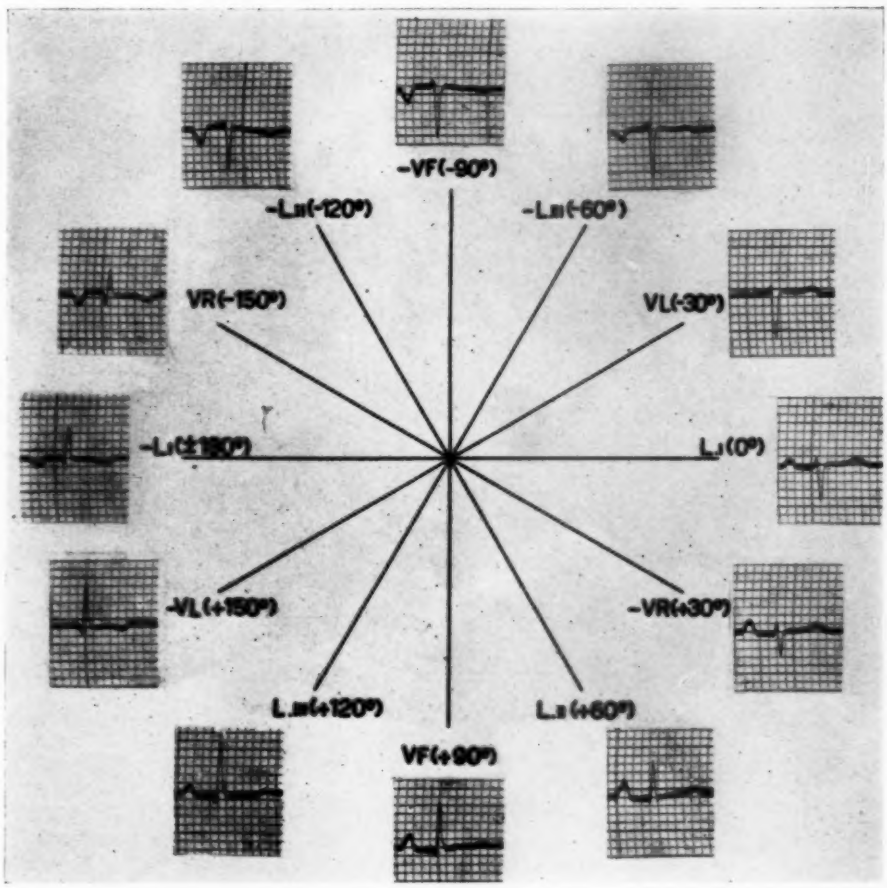

Fig. 2.—The standard and unipolar limb leads have been registered as usual and, successively, with inverted electrodes. The tracings have been arranged at the ends of the respective directional axes. Note: (a) Starting from VL and proceeding clockwise the shape of P wave, ventricular complex, and T-wave change gradually from one lead to another. (b) The −VR lead represents the morphologic bridge between Lead I and Lead II.

Second Control.—On the chest of some patients three points have been established roughly corresponding to the ends 0°, +60° and +120° of an hexaxial system ideally traced in a frontal plane passing through the two midaxillary lines. Unipolar leads recorded from such points have been compared with standard limb leads, (Figs. 5 and 6). The following points must be noted.

(a) The coordinates of the three points are:

0° (Lead I) = IV intercostal space on the left midaxillary line,
+60° (Lead II) = XI rib on the left midaxillary line,
+120° (Lead III) = XI rib on the right midaxillary line.

These coordinates are empirically determined and not strictly constant. Their variability probably depends on the form of the chest, on the position of the heart, and on the distortion of the electric field caused by the nonhomogeneity of the conductive media. Yet such variability is not wide, and small displacements of the exploring electrode are sufficient to identify the point from which the expected tracing can be registered.

(b) The three tracings unipolarly recorded are identical in shape to the three standard limb leads. In the chest leads standardization has been empirically modified in order to obtain voltages comparable to those recorded in the limb leads. We have marked the chest leads with the letter V (according to the international terminology for unipolar leads) followed by the symbol of the corresponding standard limb lead. Therefore, the leads registered from the points 0°, +60° and +120° have been called, respectively, $V_{L.\ I}$, $V_{L.\ II}$ and $V_{L.\ III}$.

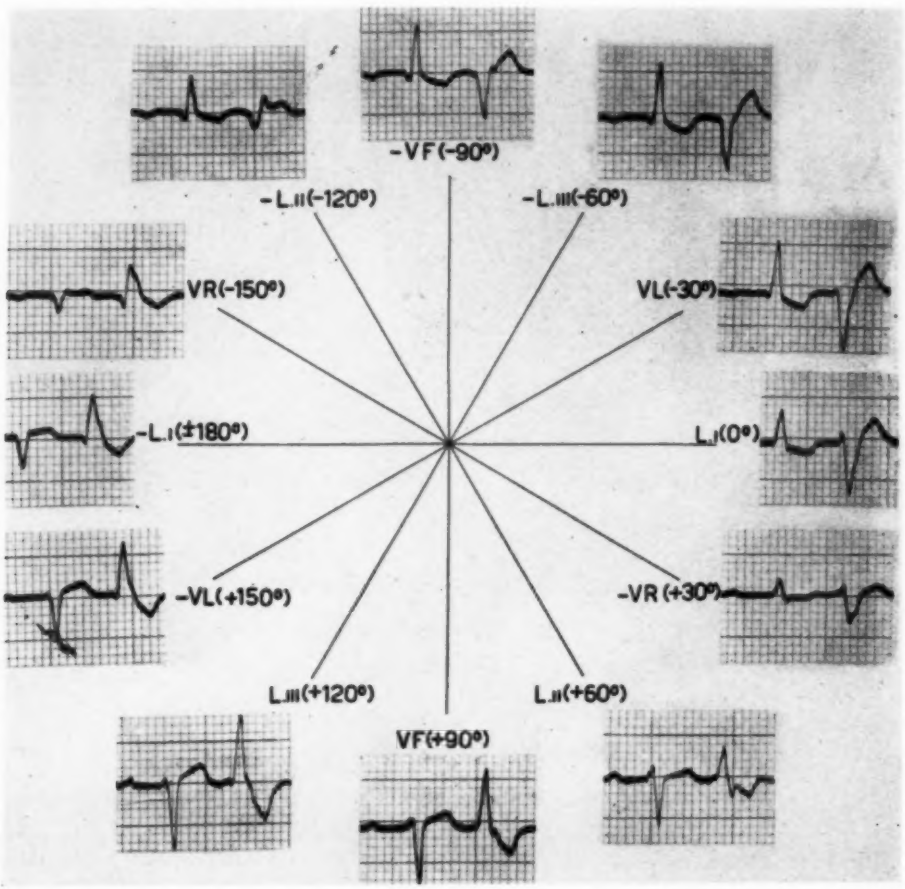

Fig. 3.—Same as in Fig. 2. Also the ventricular extrasystole changes gradually from one lead to another. Observe the resemblance between Lead III and −VL. The −VR lead represents the bridge between Lead I and Lead II.

(c) Two unipolar chest leads which for their position in the frontal plane (Fig. 1) should correspond to Leads −VR and −VL have been recorded from points of the chest wall corresponding to the ends +30° (intermediate between 0° and +60°, placed a little below the precordial point C_6) and + 150° (symmetrical to the former and placed a little below the precordial point C_{6r}). These two leads have been called, respectively, V_{-VR} and V_{-VL} (Fig. 6,*B*).

Figs. 5 and 6 show that it is possible to register tracings identical to those obtained by the standard limb leads by starting from points of the chest surface and by using a unipolar method. Moreover, the lead points are foreseen according to the theoretical assumptions discussed here and correspond to the relative ends of the hexaxial system in the frontal plane. The V_{-VR} lead is identical to the inverted unipolar lead of the right arm −VR, proving that the −VR lead is not merely the mirror image of the VR lead, but it actually corresponds to an "epicardial" lead intermediate between the unipolar Leads $V_{L.\ I}$ and $V_{L.\ II}$. The V_{-VL} lead is identical to the inverted unipolar lead of the left arm −VL, proving that at 30° more to the right of the $V_{L.\ III}$ lead point one really meets a lead equal to the mirror image of VL.

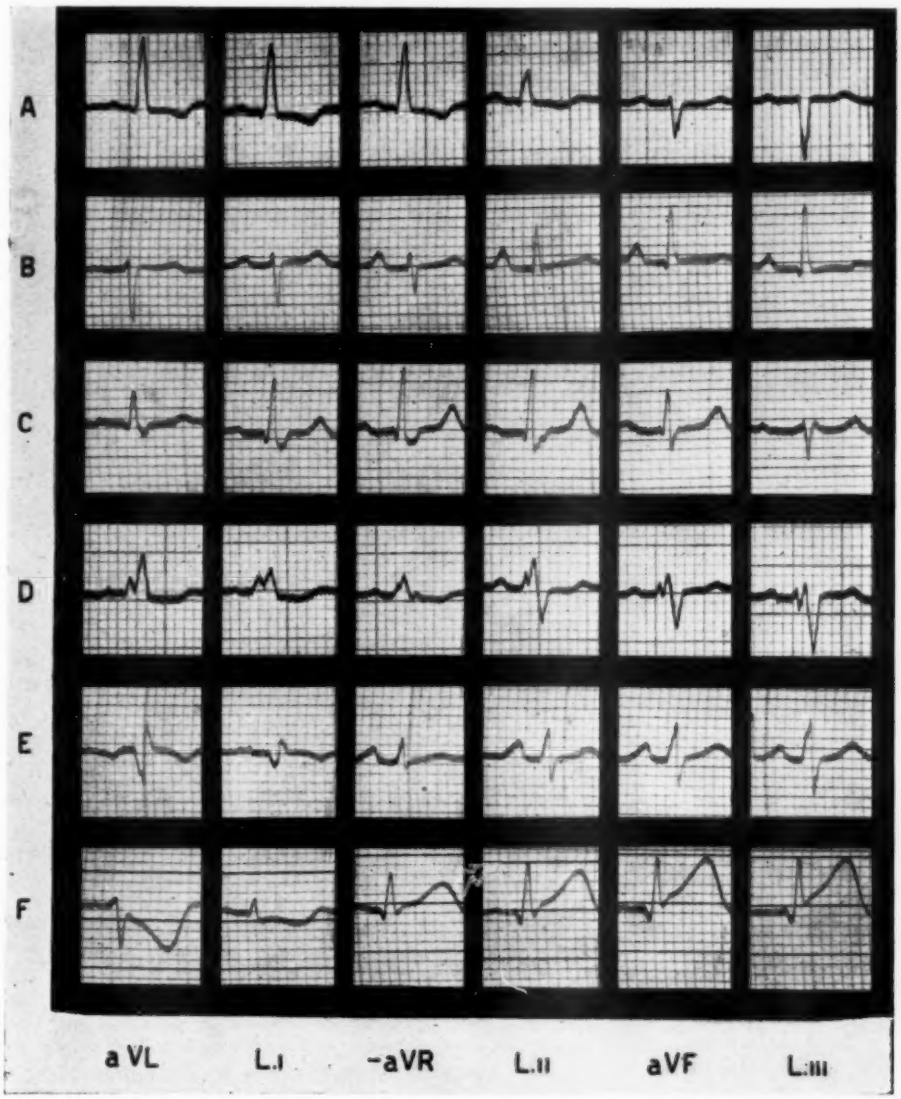

Fig. 4.—Limb leads of six cardiac subjects: rational arrangement of the leads. *A*, **Left ventricular strain.** *B*, **Right ventricular strain.** *C*, **Partial right bundle branch block.** *D*, **Left bundle branch block.** *E*, **High lateral myocardial infarction.** *F*, **Recent posterior infarction. Note: (1) The gradual transformation of every lead into the next one; (2) the insertion of the −aVR lead between Lead I and Lead II; (3) the resemblance between Lead III and the mirror image of aVL.**

Third Control.—We have proved that tracings identical to those of the standard limb leads can be registered by means of unipolar leads. Reciprocally, tracings identical to those of the unipolar limb leads can be registered by means of bipolar leads. This has been already verified as far as Goldberger's augmented unipolar limb leads are concerned. It is possible though to register tracings identical to those of the unipolar limb leads by using leads from two points of the body surface in a way quite similar to that of the standard limb leads. We have marked these leads with the letter L (meaning bipolar leads as the standard limb leads) followed by the symbol of the unipolar limb lead to which the tracing corresponds; for instance, L_{VF} means a bipolar lead whose result is equal to that of the VF unipolar lead.

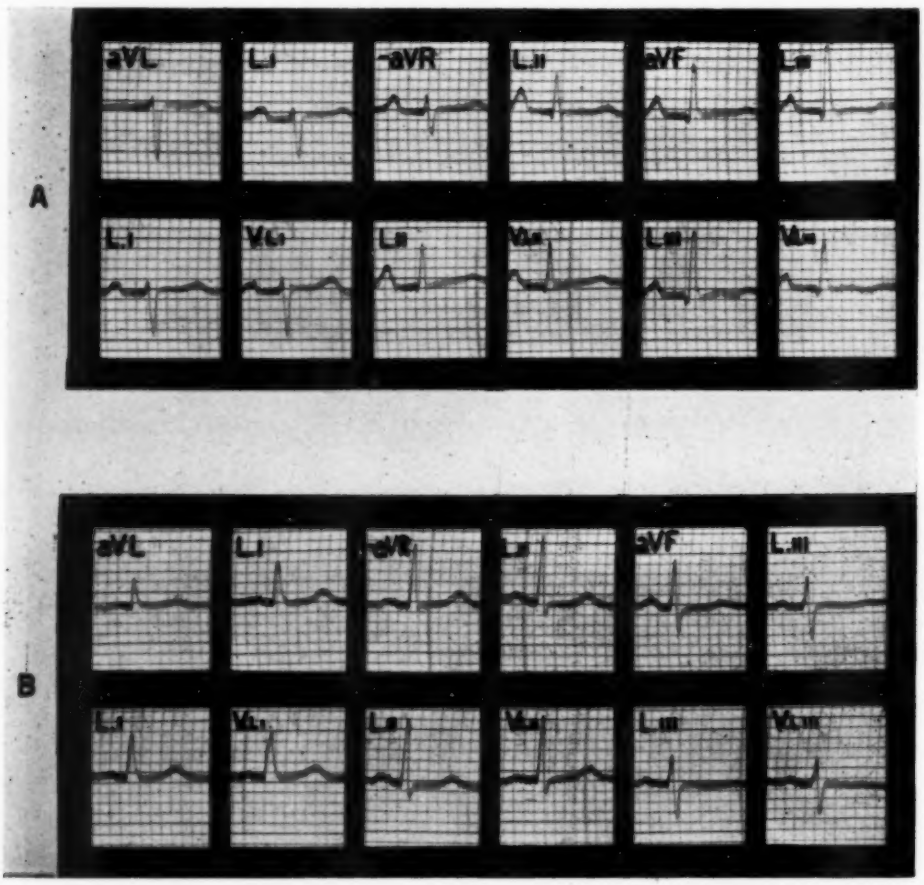

Fig. 5.—*A* and *B*. In the first row, the limb leads are arranged from aVL to Lead III; in the second row near each standard limb lead registered as usual (Leads I, II, and III) there is a lead registered unipolarly from the chest (respectively $V_{L.\ I}$, $V_{L.\ II}$, $V_{L.\ III}$). Note the resemblance between Lead I and and $V_{L.\ I}$, Lead II and $V_{L.\ II}$, Lead III and $V_{L.\ III}$. Discussed in the text.

On the chest wall of a patient three points have been established corresponding to the ends 0°, +120° and −120° of the hexaxial diagram. From the first two points (as we have already seen) one obtains unipolar leads identical in shape to those of Lead I and Lead II, respectively. From the point −120° (right supraclavicular region at the base of the neck) can be registered a unipolar tracing similar to the inverted Lead II (that is $V_{-L.\ II}$; Figs. 1 and 7). The points 0° and −120° have been connected, respectively, to the terminals of the left and right arm of the electrocardiograph and the lead selector has been turned on Lead I. The result theoretically foreseen should have been: $V_{0°} - V_{-120°} = -VR \cdot \sqrt{3}$.

This lead should have given, therefore, a tracing of the same shape as the −VR unipolar lead, that is the L_{-VR} lead. This was actually the case (Fig. 7). Likewise we have proceeded for other eads. By connecting the points +120° and 0°, respectively, to the terminals of the left and the right arm (lead selector on Lead I) we should have obtained: $V_{+120°} - V_{0°} = -VL \cdot \sqrt{3}$. That is a tracing equal in shape to the inverted VL lead but bipolarly registered (L_{-VL}). At last by connecting the points +120° and −120°, respectively, to the terminals of the left and right arm we should have obtained: $V_{+120°} - V_{-120°} = VF \cdot \sqrt{3}$, a tracing equal to that of the VF lead but bipolarly registered (L_{VF}). As Fig. 7 shows, theoretical provisions have been experimentally proved. The tracings of the unipolar limb leads can be obtained even by bipolar leads similar to those of the standard limb leads.

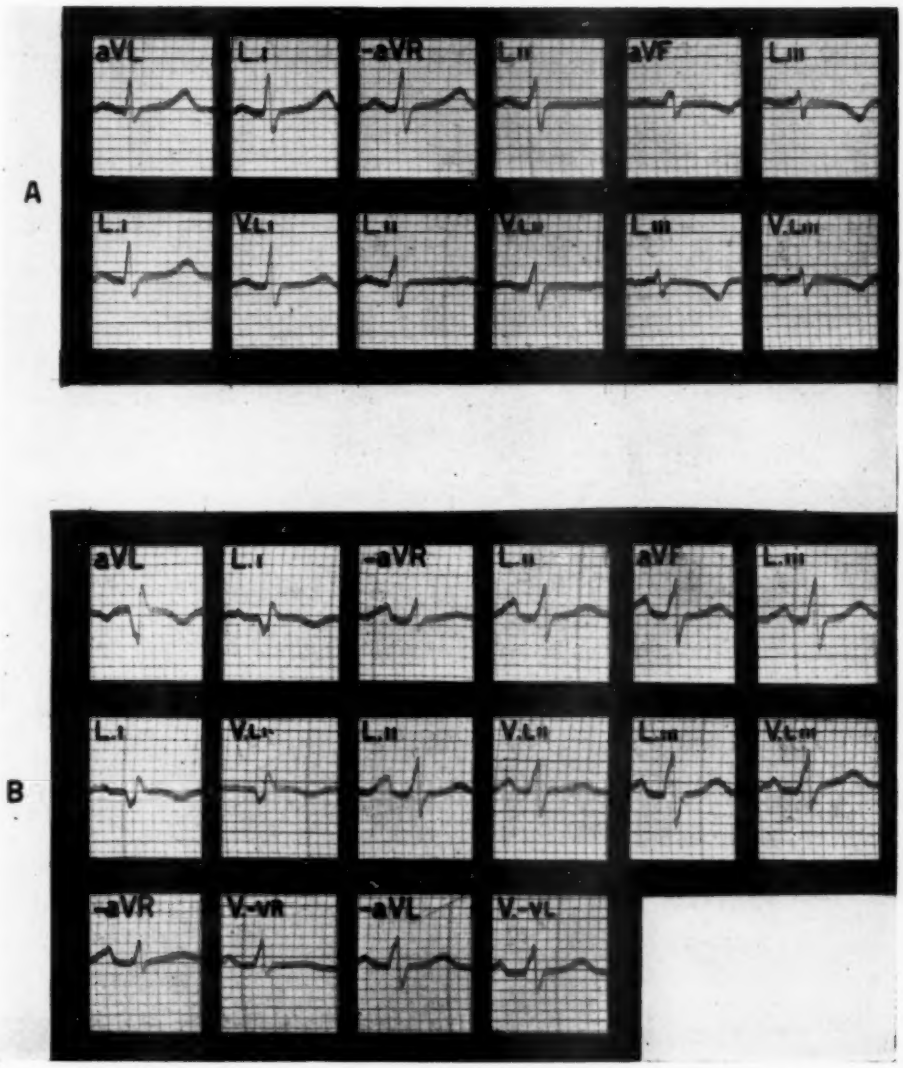

Fig. 6.—*A*, Same as for Fig. 5. *B*, First two rows, same remarks as for Fig. 5; third row: near the −aVR and −aVL leads there are two leads (V_{-VR} and V_{-VL}, respectively) unipolarly registered from points of the chest surface. Note the resemblance between −aVR and V_{-VR}; between −aVL and V_{-VL}. Discussed in the text.

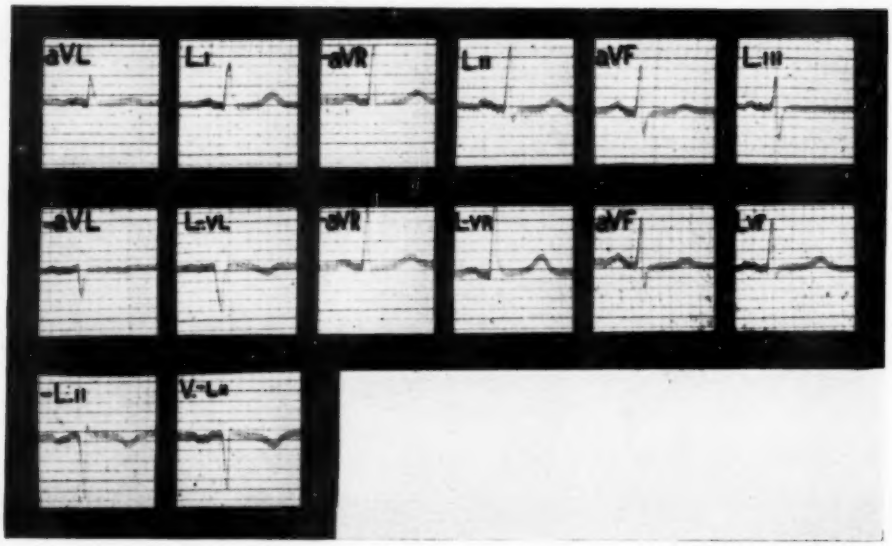

Fig. 7.—First row. Limb leads arranged from aVL to Lead III. Second row. Near the three unipolar limb leads −aVL, −aVR, and aVF there are tracings registered bipolarly from points of the chest surface (L_{-VL}, L_{-VR}, L_{VF}). Note the resemblance between the aV tracings and the leads obtained bipolarly. Third row. Near the bipolar tracing of Lead II inverted lead (−L. II) the unipolar tracing registered from a point of the chest surface. Note the resemblance between the two tracings. Discussed in the text.

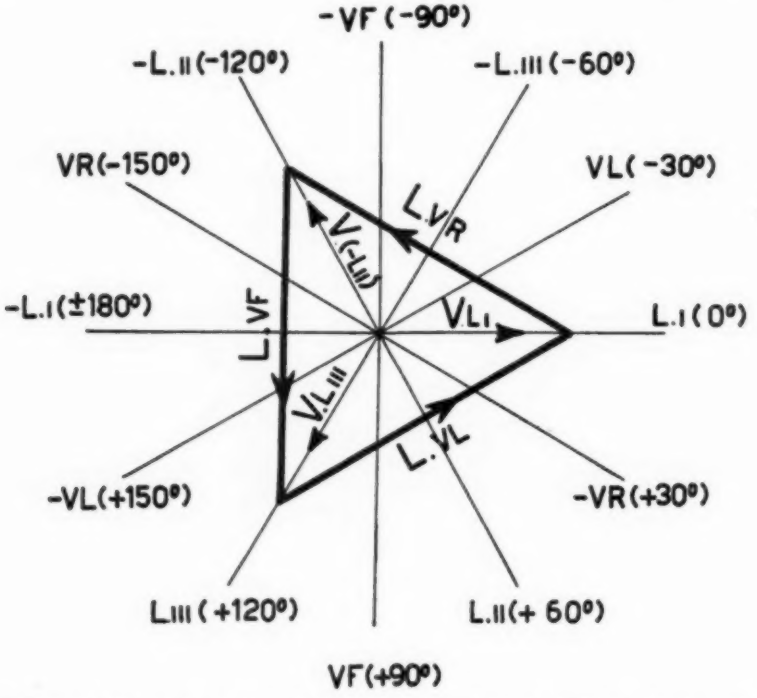

Fig. 8.—Hexaxial diagram in the frontal plane. We see a triangle similar to Einthoven's but clockwise rotated 30°. If we apply the electrodes to the three apices of this triangle, we bipolarly register tracings (L_{VL}, L_{VR}, L_{VF}) equal to those of the unipolar limb leads, and unipolar tracings ($V_{L.\ I}$, $V_{L.\ II}$, $V_{L.\ III}$) equal to those of the standard limb leads.

Fourth Control.—The points 0°, +120° and −120° have been established on the chest wall of some patients. These three points correspond to the vertices of a triangle similar to Einthoven's but with a clockwise rotation of 30° in the frontal plane (Fig. 8). They have been connected to the electrocardiograph in the following order: point 0° to the terminal of the right arm; point −120° to the terminal of the left arm; point +120° to the terminal of the left leg. Then six leads (three bipolar and three Goldberger's augmented leads) have been registered as if they were Einthoven's triangle. The results we expected were the following:

Lead selector on Lead I $= V_{-120°} - V_{0°} = L_{VR}$
Lead selector on Lead II $= V_{+120°} - V_{-120°} = L_{VF}$
Lead selector on Lead III $= V_{+120°} - V_{0°} = L_{-VL}$ (and with inverted polarity: L_{VL})
Lead selector on aVR $= aV_{0°} = aV_{L.\ I}$
Lead selector on aVL $= aV_{-120°} = aV_{-L.\ II}$ (and with inverted polarity: $aV_{L.\ II}$)
Lead selector on aVF $= aV_{+120°} = aV_{L.\ III}$

Then we should have obtained theoretically, by bipolar method, tracings identical to those of the conventional unipolar limb leads, and by Goldberger's "unipolar" method the aV tracings of the

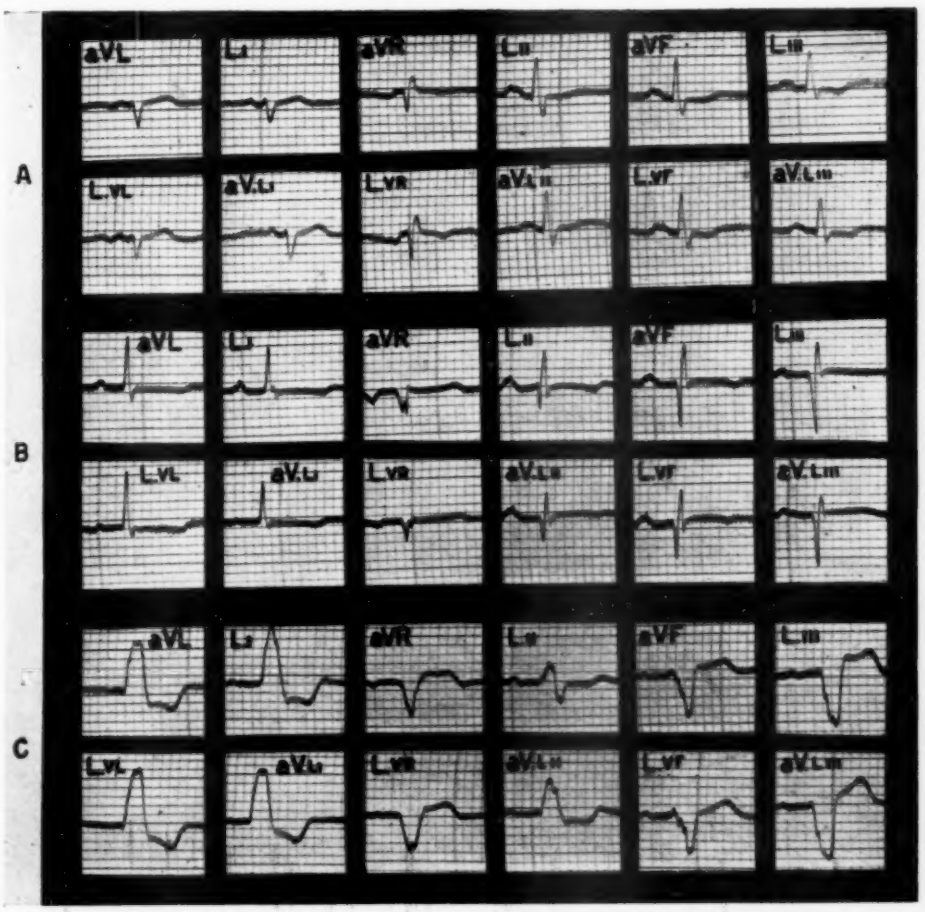

Fig. 9.—*A*, First row: limb leads arranged from aVL to Lead III (here the aVR lead has not been replaced by Lead −aVR) and registered in Einthoven's triangle. Second row: the same tracings registered on a triangle like the one of Fig. 8. The bipolar leads (L_{VL}, L_{VR}, L_{VF}) resemble the unipolar limb leads of Einthoven's triangle and the unipolar leads ($aV_{L.\ I}$, $aV_{L.\ II}$, $aV_{L.\ III}$) resemble the bipolar limb leads of Einthoven's triangle. *B* and *C*, Same observations. Discussed in the text.

standard limb leads. Fig. 9 (*A*, *B*, *C*) shows that such theoretical provisions have been experimentally confirmed. Small differences of shape found among the tracings registered by Einthoven's triangle and those registered by the new triangle are to be attributed to the difficulty of identifying exactly the point −120° but do not alter the validity of the demonstration.

DISCUSSION

All limb leads can be considered as "equivalent" to "unipolar" leads (according to the electrocardiographic meaning of this term), independently from the actual lead method. Wilson's limb leads are unipolar leads registered in the frontal plane along directions forming angles of −30° (VL), +90° (VF) and −150° (VR) with the horizontal. Goldberger's augmented limb leads are bipolar leads which give tracings equal to those unipolarly registered from the former points, the only difference being in the voltage of the complexes. Einthoven's standard limb leads are bipolar leads which give tracings equal to those that can be obtained by unipolar method along directions forming angles of 0° (Lead I), +60° (Lead II) and +120° (Lead III) with the horizontal; also in this case only the voltage of the complexes is different. Then all these leads give tracings equivalent to those of particularly "augmented" unipolar leads and whose "augmentation" ratio depends on the lead method as follows: the ratio is of 1.5:1 for Goldberger's augmented limb leads; it is 1.7:1 for Einthoven's standard limb leads; and 2:1 for Wilson's unipolar limb leads (1 mv. = 2 cm.). Therefore, there is no substantial difference among all these limb leads. It is not justified to keep the standard limb leads separated from the other leads, considering the former as "mixed" leads which need the help of the unipolar ones for a correct reading. There is no objective reason to affirm the superiority of the unipolar limb leads over the standard leads and reciprocally. All limb leads are interdependent, for they all register the same phenomenon (synthetically represented by the vectorcardiogram in the frontal plane) with results equivalent to those obtained by unipolar leads. On the other hand each lead is distinguished from the others because each one separately registers the electric phenomenon from a point of its own and, therefore, from a direction of its own in the frontal plane.

Cohen and Glicksman[2] came very near to this point of view. They believed that the unipolar limb leads represent the vectors passing through the heart while the standard limb leads would represent the vectors going tangentially to the heart. However, this interpretation is not acceptable because each lead registers, in a different degree, all the cardiac vectors. According to Meyer and Herr[3] the unipolar limb leads, even if recorded by Goldberger's method, show an amplitude lower than the standard limb leads, making less evident the details of the complexes. Obviously the different size of the complexes is related to the different rate of "augmentation" above mentioned. However, this is not sufficient to state the superiority of the standard limb leads over the unipolar leads, for it would be enough to turn slightly the volume switch of the electrocardiograph to avoid and even to invert this superiority (and this actually is the case with Wilson's unipolar limb leads, 1 mv. = 2 cm.). We agree with Minot's[19] statement that unipolar limb leads do not represent any "biological newness," but we would add that they are not useless, for they allow a more detailed exploration of the

electric behavior of the heart. According to Fiske[24] and other authors it would not be exact to define the standard limb leads as "equivalent" to unipolar limb leads because all leads (also Wilson's) are actually bipolar. The divergency is only apparent and is dependent on the meaning of the term "unipolar." Goldberger's leads are considered equivalent to unipolar leads and also the standard leads can be considered equivalent to unipolar leads. In fact both of these groups of bipolar leads give tracings equal to those obtainable by the "unipolar" method from convenient points of the body surface.

We can logically conclude that the traditional arrangement of the limb leads in two separate groups is irrational. As in the precordial unipolar leads we must respect a certain order of succession depending on the position of the exploring electrode in the horizontal plane. So also in the limb leads we have to take into account the position of the single lead point in the frontal plane. With regard to this, as we have stated in the past[4,5] and as other authors have later confirmed,[25-29] it seems advisable to replace the VR lead with the −VR.* This is justified by the following considerations:

(a) The −VR lead (+30°) fills up the interval existing between Lead I (0°) and Lead II (+60°) so that the leads of the frontal plane are all placed at regular intervals of 30°: VL (−30°), Lead I (0°), −VR (+30°), Lead II (+60°), VF (+90°), Lead III (+120°).

(b) The −VR lead is quite similar to all the other leads from the body surface, that is, it is usually formed by positive P and T waves and by QRS complexes of "epicardial" type. This allows us to employ this lead not as an "intracavitary" lead of small interest, but exactly as any other superficial lead. As we have proved the −VR lead is actually a lead which can be recorded from a convenient point of the chest (Fig. 6,*B*) intermediate between the points of Lead I and Lead II. Therefore it has the meaning of a lead facing the surface of the heart; the shape of the −VR is really intermediate between that of Lead I and Lead II even when these leads are registered by means of the conventional bipolar method.

(c) The precordial unipolar leads are arranged in an almost horizontal plane; they explore this plane along a circle-arc embracing the apex of the heart. The interval between one lead and the other is sufficiently regular. Also in the frontal plane we have six leads (unipolar or giving results equal to those of unipolar leads). As we have suggested they can be arranged along a circle-arc embracing the apex of the heart and placed at regular intervals of 30°, establishing a complete analogy between the exploration of the frontal and of the horizontal plane. All these leads can be read and interpreted by a uniform method.

(d) The traditional arrangement of the limb leads (as recently noted by Donzelot and Milovanovich[25]) is quite as unjustified as the arrangement of the precordial leads in the following order would be: V_6, V_3, V_1, $-V_4$, V_8, V_2. Such an arrangement would have no meaning for the precordial leads, likewise the traditional arrangement of the limb leads is irrational and without meaning.

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*The −aVR lead can be easily obtained by connecting the electrodes of the left arm and leg through a conductive wire and by turning the lead selector on Lead I or Lead II.

More recently Welsh[28] suggested an arrangement of the limb leads starting from Lead I and including Lead −aVR as follows: Lead I, −aVR, Lead II, aVF, Lead III, −aVL. This arrangement is based on the same assumptions as the one suggested by us, but it requires the inversion of two leads. Lead −aVL, moreover, seems not as useful as Lead aVL (for instance in the diagnosis of high lateral infarction). Graettinger and co-workers[29] have recently published a work on the same subject. Their arguments and conclusions are closely in agreement with the ones previously expressed by us.

It is impossible to report here a list, even if brief, of all the inaccuracies of reading caused by the traditional arrangement of the limb leads. Only one example will be sufficient: Yu and Blake[30] in a case with evident posterior myocardial infarction have observed a small Q_3, a very small Q_2 and no Q wave in Lead aVF. This is not likely because Lead aVF is intermediate between Lead II and Lead III and when a Q wave is present in these two leads it is present also in Lead aVF. In the same work the ratio Q/R in Lead aVF is sometimes not intermediate between those in Lead II and Lead III (Cases 14, 30, 32, 44, 78, 106). Further the same authors state that in cases of posterior myocardial infarction the Q_3 wave is determined by the Q_{aVF} (because of the transmission of the intracavitary potentials to the left leg through the necrotic region), while in cases without infarction the Q_3 wave is determined by the presence of the R wave in Lead aVL. In our opinion this interpretation is not entirely satisfactory; in fact in almost all cases (with or without posterior myocardial infarction) in which an evident Q_3 wave exists, there is also an R wave (not preceded by a Q wave) in Lead +aVL. We have only to remember that Lead III is adjacent to the −aVL lead (Fig. 1) and that if there is a Q wave in Lead III there is also a Q wave in Lead −aVL and, therefore, an R wave (not preceded by a Q wave) in Lead aVL. The Q_3 wave "depends" neither on the Q_{aVF} nor on the R_{aVL} or, at least, we could safely affirm the reciprocal. The Q_3 wave depends exclusively on the transmission of early negative potentials along the axis +120°, whether they are due to the presence of myocardial necrotic regions or merely to the position of the heart.

This exemplification could be more enlarged, but this would be quite outside the aims of this paper.

SUMMARY

1. As everybody knows, unipolar limb leads are "unipolar" leads (according to the conventional electrocardiographic meaning of this term) registered from the ends −150° (VR), −30° (VL) and +90° (VF) of the lead axes of the frontal plane. Standard limb leads, although registered by bipolar method, give the same results as unipolar leads obtained from the ends 0° (Lead I), +60° (Lead II) and +120° (Lead III) of the lead axes of the frontal plane. Theoretical and experimental data supporting this statement are presented.

2. It is unjustified, therefore, to keep these two groups of leads separate and to regard the ones as "true" and the other as "mixed" records. Standard limb leads do not need, for an accurate reading, the help of the unipolar limb leads or, at least, the reciprocal is likewise true.

3. The traditional arrangement of the limb leads is irrational. Every lead must occupy its right place according to its relative position in the frontal plane; besides, Lead VR must be replaced by Lead −VR. The only rational arrangement of the limb leads is the following: VL, Lead I, −VR, Lead II, VF, Lead III. This arrangement allows an exploration of the frontal plane thoroughly comparable to the one performed in the horizontal plane by means of unipolar precordial leads.

The author is greatly indebted to Dr. Sergio Rossi for valuable aid in translation and to Mrs. Vannina Fumagalli, B.A., for helpful assistance in the preparation of this paper.

APPENDIX

A bipolar lead recorded from points of the body surface equidistant from the heart electric center of gravity gives a result morphologically equal to the one of a "unipolar" lead recorded from a convenient point of the body surface.[4,5,12,13,31]

Even bipolar leads recorded from points of the body surface not equidistant from the heart electric center of gravity give results which can be obtained with "unipolar" leads registered from a convenient point of the body surface. A mathematical approach to this equivalence has been briefly summarized by Junghans.[31]

Here we shall give a complete theoretical demonstration. In the following discussion we suppose that the two points from which the bipolar lead is registered are placed at a sufficient distance from the heart, so that they cannot be influenced by local potentials. Such a distance must be at least of 2 to 3 cm., according to Gillmann,[11] while, according to Bohning and associates[15]: "The distance from the surface of the heart to the anterior chest wall is sufficient to minimize the effect of any small area of the heart," and then all the points of the body surface would always be at sufficient distance from the heart.

S is the plane of any bipolar lead whatsoever (that is, the plane containing the two lead points and the center of the electric field of the heart), $\vec{M}$ is the moment of a cardiac vector however orientated in the space, $\vec{m}$ is the projection of $\vec{M}$ on the plane S. The effect of $\vec{M}$ on the bipolar lead is proportional to the effect exerted on the same lead by $\vec{m}$: therefore, we shall consider only this latter one.

In Fig. 10, O is the center of the heart electric field, P and P' are such two points of the body surface that their distances from O are:

$$\overline{P'O} = r \qquad \overline{PO} = R \qquad \text{and} \qquad R > r$$

$\vec{m}$ is the projection, on the plane POP', of the moment $\vec{M}$ of a cardiac vector however orientated in the space.

A bipolar lead derived from the points P (positive electrode) and P' (negative electrode) will give the difference of potential raised by $\vec{m}$ in the points P and P', that is:

$$V^{\vec{m}}_{P'P} = V^{\vec{m}}_{P} - V^{\vec{m}}_{P'} . \tag{1}$$

Let us divide the angle $P\hat{O}P'$ in two angles β and γ by a straight line OA, so that:

$$\frac{\cos \beta}{R^2} = \frac{\cos \gamma}{r^2} \tag{2}$$

and likewise let us divide the angle $P'\hat{O}C$ (formed by $\overline{P'O}$ and the prolongation of $\overline{PO}$) in two angles δ and ε by a straight line OB so that:

$$\frac{\cos \varepsilon}{R^2} = \frac{\cos \delta}{r^2} . \tag{3}$$

Let us now decompose the moment $\vec{m}$ along the two directions OA and OB. We obtain the two components $\vec{m'}$ and $\vec{m''}$. It is possible to demonstrate that the component $\vec{m''}$ has no effect on the bipolar lead registered from the points P and P′: in fact the effect of $\vec{m''}$ on these two points is:

$$V_P^{\vec{m''}} = \vec{m''} \cdot \cos\beta \cdot \frac{3}{R^2} = 3 \cdot \vec{m''} \cdot \frac{\cos\beta}{R^2}$$

$$V_{P'}^{\vec{m''}} = \vec{m''} \cdot \cos\gamma \cdot \frac{3}{r^2} = 3 \cdot \vec{m''} \cdot \frac{\cos\gamma}{r^2}$$

then, remembering Eq. (2):

$$V_{P'P}^{\vec{m''}} = V_P^{\vec{m''}} - V_{P'}^{\vec{m''}} = 3 \cdot \vec{m''} \cdot \left\{\frac{\cos\beta}{R^2} - \frac{\cos\gamma}{r^2}\right\} = 0.$$

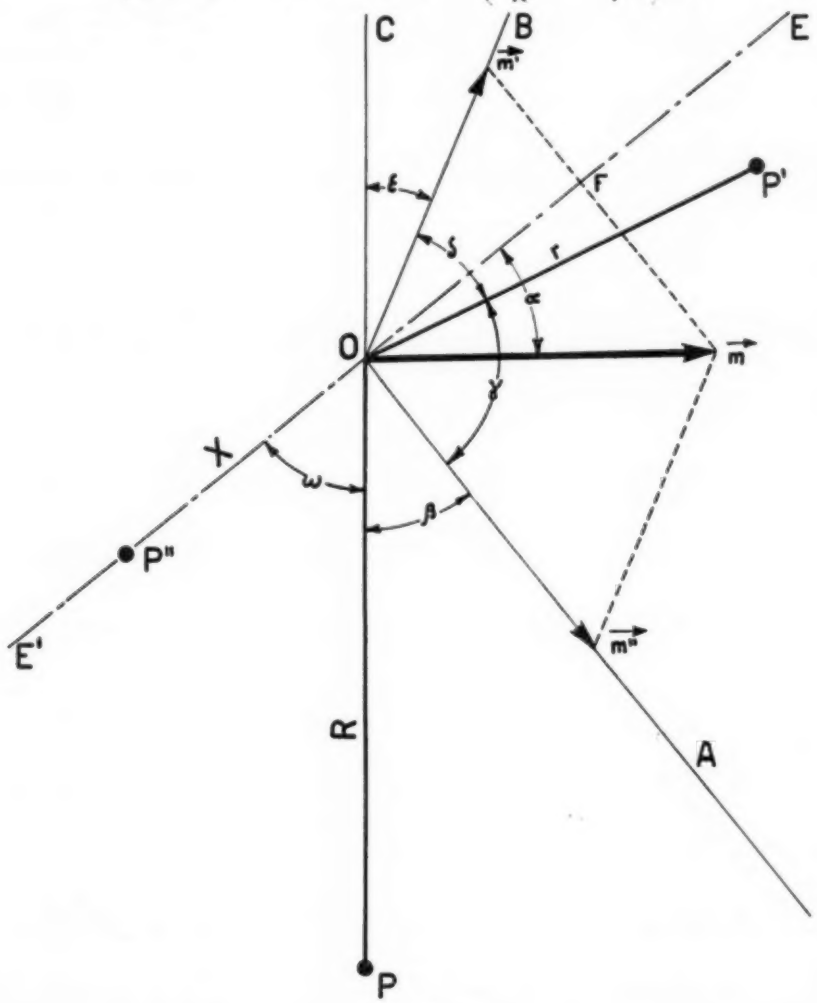

Fig. 10.

Therefore the effect of the moment $\vec{m}$ on the bipolar lead registered from the points P and P′ is equal to the effect exerted on such a lead by the only component $\vec{m'}$. This effect is evident from the following relations:

$$V_P^{\vec{m'}} = -\vec{m'} \cdot \cos\varepsilon \cdot \frac{3}{R^2} = -3 \cdot \vec{m'} \cdot \frac{\cos\varepsilon}{R^2}$$

$$V_{P'}^{\vec{m}'} = \vec{m}' \cdot \cos\delta \cdot \frac{3}{r^2} = 3 \cdot \vec{m}' \cdot \frac{\cos\delta}{r^2} = 3 \cdot \vec{m}' \cdot \frac{\cos\varepsilon}{R^2}$$

$$V_{P'P}^{\vec{m}} = V_{P'P}^{\vec{m}'} = V_{P}^{\vec{m}'} - V_{P'}^{\vec{m}'} = -6\vec{m}' \cdot \frac{\cos\varepsilon}{R^2}. \qquad (4)$$

Let us trace a straight line EE′ which, passing through O, cuts perpendicularly the line joining the vertices of $\vec{m}$ and $\vec{m}'$ (it is then perpendicular also to OA).

F is the point of intersection, α the angle which the moment $\vec{m}$ forms with EE′. We observe that:

$$OF = \vec{m} \cdot \cos\alpha \text{ and } OF = \vec{m}' \cdot \cos(\gamma + \delta - 90°) = \vec{m}' \cdot \sin(\gamma + \delta)$$

from which we deduce:

$$\vec{m} \cdot \cos\alpha = \vec{m}' \cdot \sin(\gamma + \delta) \text{ and then: } \vec{m}' = \frac{\vec{m} \cdot \cos\alpha}{\sin(\gamma + \delta)}.$$

If we replace this value in Eq. (4), we obtain:

$$V_{P'P}^{\vec{m}} = -\vec{m} \cdot \cos\alpha \cdot \frac{6\cos\varepsilon}{R^2 \cdot \sin(\gamma + \delta)}$$

Since R, ε, γ, δ are constant for a given bipolar lead, whatever the value and direction of $\vec{m}$ may be, we can conclude:

$$V_{P'P}^{\vec{m}} = \vec{m} \cdot \cos\alpha \cdot K \quad \text{Eq. (5)}, \quad \text{in which } K = -\frac{6\cos\varepsilon}{R^2 \cdot \sin(\gamma + \delta)}.$$

Eq. (5) means the effect that the moment $\vec{m}$ of any vector contained in the plane POP′ exerts on the bipolar lead registered from the points P and P′.

Let us now suppose P″ a point of the body surface placed on the straight line EE′, at a distance $\overline{P''O} = X$ from the electric center of gravity O, and let us calculate the effect that the moment $\vec{m}$ would have on a unipolar lead registered from the point P″:

$$V_{P''}^{\vec{m}} = -\vec{m} \cdot \cos\alpha \cdot \frac{3}{X^2}.$$

Since the distance X is constant for the unipolar lead registered from the point P″, whatever the direction and value of $\vec{m}$ may be, the last equation is:

$$V_{P''}^{\vec{m}} = \vec{m} \cdot \cos\alpha \cdot K', \text{ Eq. (6) in which } K' = -\frac{3}{X^2}.$$

The comparison between Eq. (5) and Eq. (6) enables us to establish the following relation:

$$\frac{V_{P'P}^{\vec{m}}}{V_{P''}^{\vec{m}}} = \frac{K}{K'} = \text{Const., Eq. (7) in which Const.} = \frac{2X^2 \cdot \cos\varepsilon}{R^2 \cdot \sin(\gamma + \delta)}.$$

Eq. (7) tells us that the moment $\vec{m}$ of a vector, of any size and orientation in the plane POP′, exerts on the bipolar lead registered from the points P and P′ an effect proportional to the one exerted on the unipolar lead registered from the point P″. If we extend this relation to all the instantaneous vectors of a cardiac cycle, we may conclude that the potentials bipolarly derived from P and P′ are proportional to those derived unipolarly from P″: in other words the two electrocardiographic tracings, the bipolar and the unipolar ones, are identical in shape and different only in voltage. If the distance X of the point P″ from the electric center of gravity *O* is chosen so that:

$X = R \cdot \sqrt{\frac{\sin(\gamma + \delta)}{2 \cdot \cos\varepsilon}}$ we have: Const. = 1 and Eq. (7) becomes: $V_{P'P}^{\vec{m}} = V_{P''}^{\vec{m}}$ that is the two tracings, bipolar and unipolar, are exactly equal not only in shape but also in voltage.

The axis EE′ of the unipolar lead can be defined not only geometrically (as reported above) but also trigonometrically. In fact it is sufficient to determine the angle ω which the straight line EE′ forms with the straight one PC. To this purpose we remember that:

$$\beta = 90° - \omega \quad \text{and that} \quad \gamma = P\hat{O}P' - (90° - \omega).$$

Replacing these values in Eq. (2), we have:

$$\frac{\cos (90° - \omega)}{R^2} = \frac{\cos (P\hat{O}P' - 90° + \omega)}{r^2} \quad \text{from which}$$

$$r^2 \cdot \sin \omega = R^2 \cdot \sin (P\hat{O}P' + \omega)$$

$$r^2 \cdot \sin \omega = R^2 \cdot \sin P\hat{O}P' \cdot \cos \omega + R^2 \cdot \cos P\hat{O}P' \cdot \sin \omega$$

and dividing both members of the equivalence by $\cos \omega$:

$$r^2 \cdot \tan \omega = R^2 \cdot \sin P\hat{O}P' + R^2 \cdot \cos P\hat{O}P' \cdot \tan \omega, \text{ from which}$$

$$\tan \omega = \frac{R^2 \cdot \sin POP'}{r^2 - R^2 \cdot \cos P\hat{O}P'}. \qquad (8)$$

The angle ω is then determined in function of the angle $P\hat{O}P'$ and of the distances R and r between the electric center of gravity *O* and the points P and P′.

Particular Case.—If the points P,P′, and P″ were equidistant from the center *O*, that is $PO = P'O = X = R$ and the angle $P\hat{O}P' = 120°$, it would be:

$$\beta = \gamma = 60° \qquad \text{and} \qquad \delta = \varepsilon = 30°.$$

In such a case, Eq. (7) and Eq. (8) would become:

$$\frac{V_{P'P}^{\vec{m}}}{V_{P''}^{\vec{m}}} = \frac{2 \cdot \cos 30°}{\sin 90°} = \sqrt{3} \quad \text{from which} \quad V_{P'P}^{\vec{m}} = V_{P''}^{\vec{m}} \cdot \sqrt{3}$$

$$\tan \omega = \frac{\sin 120°}{1 - \cos 120°} = \frac{\sqrt{3}}{3} \quad \text{from which} \quad \omega = 30°.$$

This is just the case of the standard bipolar limb leads, which give the same result as unipolar leads (particularly "augmented": augmentation ratio 1.7:1) registered along a directional axis forming an angle ω of 30°.

Example from Fig. 1:

$$\text{Lead III} = VF - VL = V_{+120°} \cdot \sqrt{3}.$$

That is, the bipolar lead Lead III is equal to a unipolar lead registered on the axis +120° (forming an angle $\omega = 30°$ with the axis of Lead VF), and "augmented" according to the ratio 1.7:1.

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THE DIRECTION OF MEAN QRS AND T VECTORS

I. Einthoven Frontal Plane

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USING the technique of measuring the areas enclosed by the scalar QRS and T configurations of two Einthoven standard leads, Ashman and Byer carried out fundamental investigations on the magnitudes and directions of the mean frontal QRS and T vectors and their vector sum, the frontal ventricular gradient.[1,2] Recently a simple, practical method of estimating the direction of mean manifest electrocardiographic vectors from the location of the transitional zone has been described.[3,4] The purpose of the present study was to reinvestigate the normal range of angular position of mean manifest frontal QRS and T vectors as measured by this simple technique and to set up quantitative standards by which certain borderline extremity leads might be separated more accurately into normal and abnormal groups.

Although recent publications on spatial vector electrocardiography[3,5] have described the use of precordial leads for determining the direction of mean vectors, there are several practical as well as theoretical limitations to this technique. Previous investigation has shown that the spatial QRS-T angle, estimated by means of the six extremity leads and the six precordial leads of the routinely recorded electrocardiogram, normally may be relatively large,[6] and further study indicated that overlapping of normal and abnormal values is much greater with the spatial than with the frontal QRS-T angle when precordial leads are used in the estimation of the former. Moreover, recent studies with vectorcardiographic lead derivations,[7] as well as an analysis to be published of the effect of dipole eccentricity on the direction of lead axes, demonstrated certain inherent errors in the use of the transitional patterns of semidirect leads for estimating the direction of mean vectors.

Recent investigation in this laboratory has demonstrated the practical feasibility of supplementing the twelve routinely recorded extremity and precordial leads with six additional leads obtained from a modification of Arrighi's sagittal triangle.[8] The Einthoven and Arrighi triangles are then used for the study of both planar and spatial mean vectors[6,9]; the precordial leads are utilized primarily for a more detailed electrocardiographic exploration of the underlying

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myocardium[7] rather than for vector analysis. While more data are being collected with the Arrighi triangle, an analysis of frontal vector projections based upon tracings recorded with the Einthoven triangle has been carried out. This constitutes the material presented in this first paper.

MATERIAL AND METHODS

Over 300 electrocardiograms, previously interpreted as being normal, were drawn in a random manner from the electrocardiographic files of the Cincinnati General Hospital. All tracings had been recorded on separate patients with a direct writing Sandborn Viso-Cardiette and consisted of Leads I, II, III, aV_R, aV_L, aV_F, and V_1 through V_6. All were rechecked and only those tracings which were unequivocally normal by conventional criteria[10] were selected for final consideration. When more than one electrocardiogram existed for a single patient, no one tracing was chosen to be included in this series unless all were normal and entirely comparable in appearance.

The angular positions of the frontal projections of the mean QRS and T vectors of all tracings were carefully determined by the transitional zone technique described in detail by Graettinger and associates[4] and were expressed to the closest five degrees. The positive portion of the axis of Lead I was considered to be the zero axis of the frontal hexaxial reference diagram. Positive and negative angles were measured up to 180° in clockwise and counterclockwise directions, respectively.

The frontal QRS-T angle was calculated simply as the difference between the angular positions of the frontal projections of the mean QRS and T vectors. According to Graybiel and associates[11] this rarely exceeds 50° in a normal individual. It seemed desirable to use the QRS-T angle as another criterion for the selection of normal electrocardiograms for this study. However, since the validity of the QRS-T angle measurement as a criterion of electrocardiographic normality might be questioned, the clinical records of all patients demonstrating frontal QRS-T angles exceeding 50° were examined, and those tracings of patients in whom a sufficiently complete examination revealed no other evidence of heart disease were not excluded from a group of 300 finally chosen for statistical study. The clinical status of the patient was otherwise not considered, however, in selecting a tracing for the following reasons*: (1) The purpose of the study was to set up standards which would express certain accepted qualitative critera[10] for the normality of extremity leads in quantitative terms. (2) It is well known that cardiac abnormalities may exist in the presence of a normal electrocardiogram. (3) It is impossible by any methods now available, to rule out myocardial abnormality in certain individuals, particularly those who are elderly. Therefore, the final group of 300 tracings, obtained from 177 males and 123 females ranging in age from 5 to 91, included only those which (1) were normal by conventional criteria,[10] (2) demonstrated a frontal QRS-T angle of 50° or less, or (3) were obtained from individuals who had no demonstrable cardiac abnormalities despite a frontal QRS-T angle exceeding 50°.

*See also Kossmann's recent discussion of the distinction which must be drawn between the normal electrocardiogram and the normal heart.[24]

TABLE I. MEAN, STANDARD DEVIATION AND

TOTAL NO. RECORDS	SEX GROUPS		AGE GROUPS								PRECORDIAL GROUPS			
	M	F	5 TO 12	13 TO 20	21 TO 30	31 TO 40	41 TO 50	51 TO 60	61 TO 70	71+	V_1	V_2	V_3	V_4
300	177	123	26	33	43	36	58	42	33	29	9	90	155	45
177	177	0	17	16	21	20	41	28	16	18	7	49	88	33
123	0	123	9	17	22	16	17	14	17	11	2	41	67	12
26	17	9	26	0	0	0	0	0	0	0	1	7	16	2
33	16	17	0	33	0	0	0	0	0	0	0	13	13	7
43	21	22	0	0	43	0	0	0	0	0	3	17	14	9
36	20	16	0	0	0	36	0	0	0	0	0	9	25	2
58	41	17	0	0	0	0	58	0	0	0	1	14	31	12
42	28	14	0	0	0	0	0	42	0	0	2	15	19	6
33	16	17	0	0	0	0	0	0	33	0	0	11	18	4
29	18	11	0	0	0	0	0	0	0	29	2	4	19	3
9	7	2	1	0	3	0	1	2	0	2	9	0	0	0
90	49	41	7	13	17	9	14	15	11	4	0	90	0	0
155	88	67	16	13	14	25	31	19	18	19	0	0	155	0
45	33	12	2	7	9	2	12	6	4	3	0	0	0	45

The frontal QRS:T and (QRS)-(T) angles are given for all of the records and for each of the sex, age, and precordial groups. The number of records in each group is also listed. See text.

The precordial leads were examined for the location of the transitional QRS. This location was not given an angular designation[6] but was referred to by the lead, i.e., V_1 through V_6, in which the area of QRS above the base line most closely approximated the area below the base line. This was tabulated for each tracing. The location of the precordial T transitional pattern was not designated, however, since, in all of the adult tracings which made up the bulk of the series, this was closest to V_1.

Four separate entities were subjected to statistical analysis:

1. The angular position of the frontal plane projection of the mean QRS vector. This will be designated hereafter as QRS.

2. The angular position of the frontal plane projection of the mean T vector. This will be designated as T.

3. The angle on the frontal plane formed by the intersection of the projections of the mean QRS and T vectors. This angle was determined simply as the angular difference between QRS and T regardless of which was the larger and, for convenience, will hereafter be designated as QRS:T.

RANGE OF FRONTAL QRS AND T VECTORS

MEAN				STANDARD DEVIATION				RANGE			
QRS (DEGREE)	T (DEGREE)	QRS:T (DEGREE)	(QRS)-(T) (DEGREE)	QRS (DEGREE)	T (DEGREE)	QRS:T (DEGREE)	(QRS)-(T) (DEGREE)	QRS (DEGREE)	T (DEGREE)	QRS:T (DEGREE)	(QRS)-(T) (DEGREE)
43.2	41.4	17.4	1.8	27.6	20.2	13.8	22.2	−30 to 95	0 to 90	0 to 75	−45 to 75
49.0	44.9	17.1	4.0	27.2	21.0	14.1	21.8	−30 to 95	−15 to 90	0 to 75	−45 to 75
35.0	36.4	17.8	−1.5	26.2	17.9	13.5	22.3	−30 to 85	0 to 80	0 to 45	−45 to 50
54.8	39.4	25.0	15.4	24.8	16.7	16.4	26.0	0 to 90	0 to 70	0 to 75	−40 to 75
52.3	40.2	19.4	12.1	21.8	11.4	15.4	21.8	0 to 85	5 to 60	0 to 65	−35 to 65
50.6	43.3	19.0	7.3	25.6	20.7	11.6	21.1	0 to 95	−15 to 80	0 to 45	−30 to 45
42.5	40.1	15.4	2.4	27.0	18.9	13.8	20.7	−20 to 95	−10 to 80	0 to 35	−45 to 35
43.5	42.1	18.7	1.5	31.9	23.9	14.5	23.7	−30 to 90	0 to 90	0 to 65	−45 to 65
36.4	39.0	14.3	−2.6	28.2	21.2	11.6	18.3	−20 to 80	0 to 75	0 to 50	−35 to 50
35.8	47.1	15.9	−11.4	25.9	20.9	14.1	18.0	−10 to 80	0 to 85	0 to 45	−45 to 20
30.0	39.1	12.2	−9.1	23.6	22.0	11.1	13.8	−25 to 60	−10 to 85	0 to 30	−30 to 15
47.8	48.3	9.4	−0.6	17.7	17.7	10.1	14.2	5 to 65	20 to 80	0 to 25	−25 to 25
43.1	40.4	15.9	2.6	24.1	17.5	13.9	21.1	−20 to 90	0 to 80	0 to 65	−45 to 65
41.5	40.9	17.1	0.4	28.8	21.9	13.3	21.7	−30 to 90	−15 to 85	0 to 50	−45 to 50
49.9	43.9	23.7	6.1	29.6	20.5	15.1	27.6	−25 to 95	0 to 90	0 to 75	−45 to 75

4. The same angle on the frontal plane formed by the intersection of QRS and T but calculated algebraically by the expression (QRS) − (T). When such an angle is positive it indicates that QRS is located in a position clockwise (i.e., to the patient's right) with respect to T; when negative, QRS is counterclockwise (i.e., to the patient's left) with respect to T. The angle between QRS and T calculated in this manner will hereafter be designated as (QRS) − (T) to distinguish it from QRS:T in which the sign is disregarded.

For statistical purposes the 300 records were arbitrarily divided into the following groups:

1. Two sex groups.
2. Eight age groups (5-12, 13-20, 21-30, 31-40, 41-50, 51-60, 61-70, 71 and older).
3. Four precordial groups, designated V_1, V_2, V_3, or V_4, depending upon the location of the QRS transitional pattern in the conventional chest leads. Of the 300 tracings 299 fell into these four groups. One tracing showed a QRS transitional pattern in V_5. This record was not considered in the statistics involving precordial groups.

Significant probabilities are designated as follows: *five per cent to 1 per cent; **1 per cent to 0.1 per cent; ***less than 0.1 per cent. Standard statistical methods are used throughout.[12]

STATISTICAL RESULTS

Appropriate tests indicated that there was no significant sex difference in the eight age groups (heterogeneity Chi-square = 9.56; $P > 0.2$), or in the four precordial groups (heterogeneity Chi-square = 6.02; $P > 0.1$). Analyses of variance failed to demonstrate any heterogeneity of the age distribution in the two sex groups ($F = 0.51$) or in the four precordial groups ($F = 0.74$).

The results of the collected data are listed in Table I. The mean, standard deviation, and range are given for QRS, T, QRS:T and (QRS) – (T) for the total group of 300 records and for all individual sex, age, and precordial groups. The number of records in each of the individual groups is also given.

Analyses of variance were carried out to determine whether there were significant differences in the means among the various groups, the following values of F being obtained:

	QRS	T	QRS:T	(QRS) – (T)
Two sex groups	19.90***	13.46***	0.16	4.52*
Eight age groups	3.44**	0.64	2.50*	6.43***
Four precordial groups	1.18	0.66	4.50**	0.83

Thus the means of both QRS and T demonstrated highly significant differences in the two sexes, and (QRS) − (T) showed a significant but much less striking difference. Age significantly influenced all of the vector measurements except T. Significant differences in the precordial groups occurred only with the QRS:T measurement.

It thus became apparent that fiducial limits could be set up for the position of T vector in each sex group. These are given in Table II. It seemed inappropriate, however, to calculate fiducial limits for the QRS:T angle unless such limits were set up for each age group and for each precordial group.

TABLE II. FIDUCIAL LIMITS FOR POSITION OF FRONTAL PLANE PROJECTIONS OF MEAN SPATIAL T VECTOR FOR INDIVIDUALS, AGE 5 AND OLDER (SEE TEXT)

	5 PER CENT FIDUCIAL LIMITS OF PREDICTED T POSITION	1 PER CENT FIDUCIAL LIMITS OF PREDICTED T POSITION
Males	3° to 86°	−10° to 100°
Females	1° to 72°	−10° to 83°

In the case of QRS and (QRS) − (T), graphing of the data suggested that a linear relation might exist between each of these quantities and age. Before pursuing this possibility further, suitable analyses of covariance were carried

out to determine whether the factors of sex or precordial QRS transitional zone influence such regressions. The F values obtained are as follows:

	REGRESSION OF QRS ON AGE	REGRESSION OF (QRS)–(T) ON AGE
Two sex groups	0.53	1.40
Four precordial groups	1.47	1.78

The relatively low values of F did not approach statistical significance, suggesting that all 300 records might be used in calculating the following regressions, both of which were highly significant as demonstrated by the t test:

$$\text{QRS} = 58° - (\text{Age} \times 0.35°) \qquad (t = 4.71^{***})$$
$$(\text{QRS}) - (\text{T}) = 17° - (\text{Age} \times 0.37°) \qquad (t = 6.43^{***})$$

The standard errors of QRS and (QRS) − (T) for a randomly chosen age are $\sqrt{715.77° + 0.0056° (\text{Age} - 42)^2}$ and $\sqrt{434.94° + 0.0034° (\text{Age} - 42)^2}$ respectively. Since in each case the second term under the radical sign is quite small when compared with the first, the former may be omitted without affecting even the 1 per cent fiducial limits significantly (less than 1° maximum). The regressions and their fiducial limits, therefore, may be combined and expressed simply as shown in Table III.

TABLE III. FIDUCIAL LIMITS FOR REGRESSIONS OF FRONTAL QRS POSITION ON AGE AND OF FRONTAL (QRS) - (T) ANGLE ON AGE FOR ALL INDIVIDUALS, AGE 5 AND OLDER
(See text)

	5 PER CENT FIDUCIAL LIMITS	1 PER CENT FIDUCIAL LIMITS
Predicted QRS position	(5° to 111°)—Age × 0.35°	(−11° to 127°)—Age × 0.35°
Predicted (QRS) - (T) angle	(−24° to 59°)—Age × 0.37°	(−37° to 71°)—Age × 0.37°

Unlike the effect of age on the position of QRS, there is no semblance of a linear relation between age and the position of T in either sex (Males: $t = 0.17$; Females: $t = 0.06$).

Since it is likely that the forces involved in repolarization are normally at least partially dependent upon those of depolarization, it also seemed appropriate to explore the possible existence of a significant regression of T on QRS. Analyses of covariance demonstrated that such a regression involving all age groups would be invalid for the male sex ($F = 2.46^{*}$) although relatively satisfactory for the female ($F = 1.05$). However, with the elimination of the two lower age groups, very satisfactory homogeneity was demonstrated for each sex (Male: $F = 0.74$; Female: $F = 0.59$). Analyses of covariance for the regression of T on QRS were then carried out for the sex, age, and precordial groups of the 241 records of patients over twenty years of age. Absence of significant heterogeneity among the groups is demonstrated by the following values of F.

	REGRESSION OF T ON QRS
Two sex groups	2.04
Six age groups	1.04
Four precordial groups	1.01

A regression of T on QRS was, therefore, calculated for the 241 records; the t test demonstrated that the equation is highly significant, a t value of only 3.36 being necessary to achieve 0.1 per cent probability.

$$T = 20.9° + (QRS \times 0.514°) \qquad (t = 14.06^{***})$$

The standard error of T for a randomly chosen QRS is

$$\sqrt{255.16° + 0.037° \quad (QRS \quad - \quad 40.7)^2}.$$

The fiducial limits of T for any QRS expressed to the closest 5° between −30° and +90° are given in Table IV.

TABLE IV. FIDUCIAL LIMITS FOR REGRESSION OF FRONTAL T POSITION ON FRONTAL QRS POSITION FOR ALL INDIVIDUALS EXCEEDING 20 YEARS OF AGE

RANDOMLY CHOSEN QRS POSITION (DEGREES)	5 PER CENT FIDUCIAL LIMITS OF PREDICTED T POSITION (DEGREES)	1 PER CENT FIDUCIAL LIMITS OF PREDICTED T POSITION (DEGREES)
−30	−36 to 47	−49 to 60
−25	−32 to 48	−45 to 61
−20	−28 to 50	−41 to 62
−15	−25 to 51	−37 to 63
−10	−21 to 53	−33 to 64
−5	−18 to 54	−29 to 66
0	−14 to 56	−25 to 67
5	−11 to 58	−22 to 69
10	−8 to 60	−18 to 70
15	−4 to 62	−15 to 72
20	−1 to 64	−12 to 74
25	2 to 66	−9 to 76
30	5 to 68	−6 to 78
35	7 to 70	−3 to 81
40	10 to 73	0 to 83
45	12 to 76	2 to 86
50	15 to 78	5 to 88
55	17 to 81	7 to 91
60	19 to 84	9 to 94
65	22 to 87	11 to 98
70	24 to 90	13 to 101
75	25 to 93	15 to 104
80	27 to 97	16 to 108
85	29 to 100	18 to 112
90	31 to 104	19 to 115

DISCUSSION

In the evaluation of conventional frontal plane Leads I, II, III, aV_R, aV_L and aV_F, possible applications of the data given above may be summarized as follows.

1. The frontal projection of the mean QRS vector may normally deviate through a wide positional range but, by the application of the regression given in Table III, the limits may be defined on the basis of age. These limits should in effect define the probability of abnormality of a given degree of left- or right-axis deviation. Since an abnormal degree of right-axis deviation may represent one of the early manifestations of right ventricular preponderance,[13] this simple regression may find useful clinical application.

2. The limits for the position of the frontal projection of the mean T vector, defined in Table II, provide easily remembered criteria for determining whether a T vector is located in a grossly abnormal position. The more complicated Table IV, however, defines the limits of T position with greater accuracy.

3. The regression (Table III) for the prediction of the limits of (QRS) − (T) takes into account the relationship of the positions of the frontal QRS and T projections with respect to each other, a concept which has not been emphasized in the literature dealing with the angle between QRS and T. The practical utility of this concept deserves investigation.

4. The relationship between the positions of frontal QRS and T projections is probably best expressed by the limits given in Table IV, as suggested by the extremely high degree of significance of the regression upon which they are based. With this table at hand, the electrocardiographer can easily determine the probability of the position of T falling outside the range of normal for a given position of QRS. The reader should note that the table is applicable only to subjects over 20 years of age.

Based upon the data analyzed above, the following objections may be raised to the use of the frontal QRS:T angle as a criterion for abnormality of extremity leads:

1. The frontal QRS:T angle is influenced by the location of the precordial transitional QRS pattern, which would necessitate separate standards for each precordial group.

2. Any designated upper limit of normal (e.g., 50°) for the frontal QRS:T angle[11] may be too large when T is located on one side of QRS and too small when T is located on the other side of QRS. Table IV shows that this asymetrical distribution of the frontal QRS:T angle obtains particularly when QRS is in either a relatively horizontal or a relatively vertical position. Since tracings with frontal QRS:T angles exceeding 50° were utilized in this statistical study only in the complete absence of other manifestations of cardiac abnormality, Table IV demonstrates the fallacy of designating a single upper limit of normal for this angle.

In addition to the formulation of standards for the angular positions of frontal plane projections of mean QRS and T vectors, the present investigation provides additional evidence dealing with the controversial question of the electrocardiographic recognition of rotation of the heart about its longitudinal axis. The location of the precordial transitional QRS pattern has been used to predict clockwise and counterclockwise cardiac rotation.[14-16] However, multiple anterior, lateral, and posterior chest leads have shown[17,18] that the contour of the line joining transitional QRS patterns in practically all instances cannot conceivably be located anatomically over the interventricular groove or on the plane of the interventricular septum. Nevertheless, such findings do not rule out the possibility that the transitional QRS pattern, when recorded in one of the six conventional precordial leads, may be correlated, perhaps empirically, with the degree of anatomic rotation. A study utilizing angiocardiographic measurements as a method of estimating cardiac rotation in vivo suggested that such a correlation does, in fact, exist.[19] Failure to demonstrate significant variation in rotation of hearts at autopsy[20] does not necessarily mitigate against

such a concept; slight changes in actual anatomic position could be associated with definite changes in electrical position in such a manner that a highly significant positive correlation might exist.

Consideration of the following facts provides additional information relative to this controversial issue. Studies of normal individuals have indicated that, while both the mean spatial QRS vector and the mean spatial T vector point more or less inferiorly, the former is invariably directed more posteriorly than the latter.[1,21-23] Clockwise rotation of the heart, as conventionally defined[15,16] should, under such circumstances, cause the frontal projection of the QRS:T angle to decrease if the mean spatial QRS vector originally is directed to the left with respect to the corresponding T vector, and to increase if the former vector is originally directed to the right with respect to the latter. Counterclockwise rotation should be manifested by opposite changes in the frontal projection of the QRS:T angle. A more convenient alternate expression of these relationships is the statement that the frontal (QRS) − (T) angle, as defined previously, should increase or become less negative with clockwise rotation and should decrease or become more negative with counterclockwise rotation of the heart.

Table I shows mean (QRS) − (T) values of −0.6°, 2.6°, 0.4° and 6.1° for the V_1, V_2, V_3, and V_4 groups, respectively. Such quantities certainly do not suggest that a progressive shift of the QRS transitional pattern from right to left across the chest is associated with increasing clockwise rotation of the heart. Moreover, as previously pointed out, analysis of variance demonstrated no significant differences among these four mean values of (QRS) − (T). ($F = 0.83$).

An objection to the foregoing interpretation might be raised in that it is conceivably possible that the varying degrees of rotation represented by the four positions of the precordial transitional patterns are so small that the positions of the frontal projections of the spatial QRS and T vectors are not significantly affected. Consideration of the mean QRS:T values of 9.4°, 15.9°, 17.1°, and 23.7° for the V_1, V_2, V_3, and V_4 groups, respectively, seems to rule out such a possibility. Analysis of variance demonstrated highly significant differences among these four means. ($F = 4.50^{**}$). Thus, it is apparent that a progressive shift of the QRS transitional pattern from right to left across the chest is associated with a significant increase in the frontal projection of the angle between the mean spatial QRS and T vectors, regardless of whether QRS is located to the right or to the left of T. It seems likely that the increasing frontal QRS:T angle is a manifestation of an increasing spatial QRS:T angle† as the mean

†By assigning assumed angular positions to the QRS vector projected on the transverse plane from the location of the precordial QRS transitional pattern, by considering the precordial T transitional zone to be located at V_1 in all of the tracings, and by using the mean positions of the frontal QRS and T vectors given in Table I, the calculated spatial QRS:T angles for the V_1, V_2, V_3, and V_4 groups are 0°, 28°, 47° and 60°, respectively.[6] Moreover, the manifestations of an increasing spatial QRS:T angle are not limited to the frontal plane since, by making the same assumptions concerning the positions of the QRS and T vector projections on the transverse plane, the average transverse QRS:T angles are 0°, 35°, 60° and 80°, and the average sagittal QRS:T angles are 0°, 40°, 67°, 76° for the V_1, V_2, V_3 and V_4 groups, respectively.[6] It should be noted that in the transverse and sagittal planes the mean QRS vector is always located posteriorly to the mean T vector so that, unlike in the frontal plane, the QRS:T and (QRS)−(T) angles are numerically identical. The individual accuracy of such calculated angles is limited since it is dependent upon assumed positions of precordial lead axes. Taken as a group, however, these calculations illustrate the general relationship of the precordial QRS transitional pattern to the magnitude of the spatial QRS:T angle and of its planar projections.

spatial QRS vector points progressively more posteriorly when the QRS transition passes successively from V_1 to V_4.

The data obtained in this study are thus interpreted by the author as evidence against the concept that the transitional pattern can be utilized to predict rotation of the heart about its longitudinal axis. The evidence seems convincing but is admittedly indirect and should not discourage further attempts to attack this controversial problem.

SUMMARY

The directions of the frontal projections of the mean spatial QRS and T vectors were determined in a group of 300 normal electrocardiograms. Analysis of these data led to the following findings and conclusions.

1. The mean angular position of the frontal QRS projection differs in the two sexes and varies with age but is not significantly influenced by the location of the QRS transitional pattern in precordial leads.

A highly significant regression of the frontal QRS position on age exists and is not influenced either by sex or by the location of the precordial QRS transition. Fiducial limits for this regression have been determined for all individuals, age 5 and older (Table III). These limits should be of value in recognizing abnormal degrees of axis deviation.

2. The mean angular position of the frontal T projection differs in the two sexes but is not significantly influenced by age or by the location of the precordial QRS transition. Fiducial limits for the frontal T position have been determined for all individuals of each sex, age 5 and older (Table II).

3. The frontal QRS:T angle is defined in this paper as the angular difference between the frontal projections of the mean spatial QRS and T vectors. The mean frontal QRS:T angle does not vary significantly in the two sexes but is influenced by age and by the location of the precordial QRS transition. Reasons for abandoning the use of this angle in clinical electrocardiography are discussed.

4. The frontal (QRS) − (T) angle is defined in this paper as the algebraic difference between the frontal projections of the mean QRS and T vectors, when a positive or negative sign is applied to each vector projection in accordance with its position on the frontal hexaxial reference diagram. The mean of this angle, which may be positive or negative, differs in the two sex groups and is profoundly influenced by age but not by the location of the precordial QRS transition. Fiducial limits for this regression have been determined for all individuals, age 5 and older (Table III).

5. A highly significant regression of frontal T position on frontal QRS position exists. This is not significantly influenced by sex, by any age over 20, or by location of the precordial QRS transition. Fiducial limits for this regression have been determined for all individuals, age 20 and older (Table IV). These limits should aid in the evaluation of extremity lead T waves when they are of borderline abnormality by conventional electrocardiographic criteria.

6. The implications of the finding that the location of the precordial QRS transition does not significantly influence the mean of the frontal (QRS) − (T) angle but does affect the mean of the frontal QRS:T angle are discussed. It is

concluded that these statistical results provide evidence against the concept that rotation of the heart about its longitudinal axis can be predicted from the location of the QRS transitional pattern in precordial leads.

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ERRORS IN UNIPOLAR LIMB LEADS CAUSED BY UNBALANCED SKIN RESISTANCES, AND A DEVICE FOR THEIR ELIMINATION

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IN recording unipolar limb leads, errors are introduced if the resistances at the limb electrodes are unbalanced. This may come about through high-skin resistance at one contact, low resistance at one contact, or any other unbalancing variation. Such dissimilar resistances are not always the result of improper preparation of the patient's skin. Those who used the hot salt water and flannel technique before pastes became available remember the not too rare patient whose skin resistance, especially at the leg, remained high, no matter what was done. Even with salt pastes the skin resistance occasionally remains high. Operators of string galvanometer electrocardiographs must be careful to keep the skin resistance low. The operator of electronically amplified electrocardiographs tends to ignore skin resistance because the apparatus does not provide for measuring skin resistance and because the high internal resistance of the machine appears to make skin resistance unimportant. Whereas skin resistance is unimportant in recording standard Leads I, II, and III, it is of distinct importance in recording augmented or nonaugmented unipolar extremity leads.

The unipolar extremity leads are unipolar in name only. They record the difference between the potential of the exploring electrode and the average potential of the points joined to form the "indifferent" electrode. The potential at the "indifferent" electrode will not be the true average if the skin resistances at the limbs are unequal. Thus, changes in potential of the "indifferent" electrode are introduced and lead to errors.

In recording aV_F, the left and right arms are joined in the lead switch to form the "indifferent" electrode, which is attached to the negative terminal of the electrocardiograph. The left leg electrode goes through the switch to the positive terminal of the machine. aV_F, therefore, represents the potential difference between the left leg and the average potential of the other two extremities. If resistance at the right arm electrode is high, preventing proper electrical contact, the electrocardiograph will record the potential difference between the left leg and left arm (standard Lead III) rather than Lead aV_F.

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On the other hand, if the skin resistance at the left arm is high, the potential difference between the left leg and right arm (standard Lead II) is recorded, rather than Lead aV_F. Fig. 1 is a diagram explaining these possible errors.

In recording Lead aV_L, the joined right arm and left leg form the "indifferent" electrode, while the localizing electrode is placed on the left arm. If the resistance at the right arm is high, the electrocardiograph records the potential difference between the left arm and the left leg, or standard Lead III inverted. If, in recording Lead aV_L, the left leg resistance is high, the electrocardiograph records the potential difference between the left arm and the right arm, or standard Lead I rather than Lead aV_L.

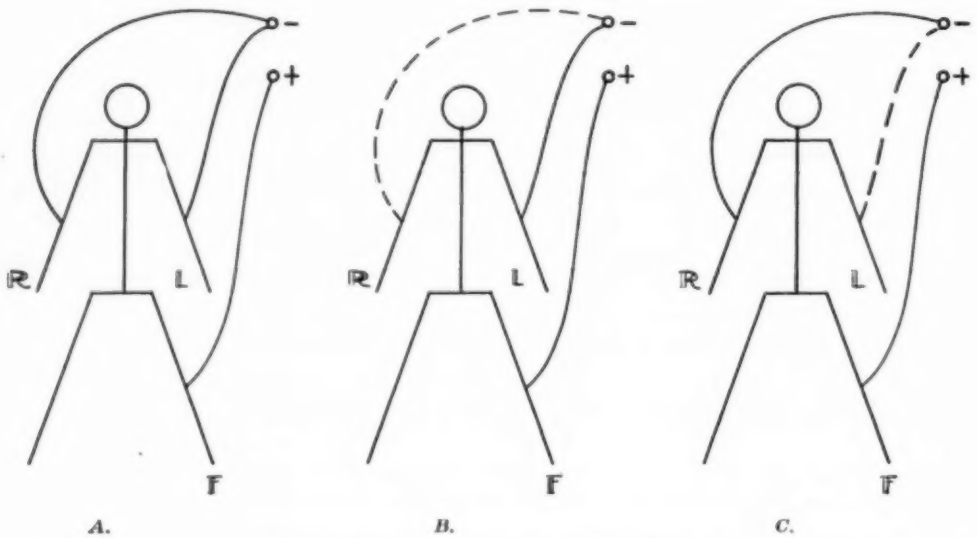

Fig. 1.—*A*, Connections for Lead aV_F. *B*, The dotted line indicates high resistance at the right arm. Therefore, the electrocardiograph records Lead III. *C*, The dotted line indicates high resistance at the left arm. The electrocardiograph records Lead II.

In recording Lead aV_R, the left arm and left leg are joined to form the "indifferent" electrode, while the localizing electrode is placed on the right arm. If the skin resistance is high at the left arm, the electrocardiograph records the potential difference between the right arm and the left leg, or standard Lead II inverted, rather than Lead aV_R. If the skin resistance is high at the left leg, the electrocardiograph records the potential difference between the right arm and left arm, or standard Lead I inverted.

The effect of unbalanced skin resistance on the nonaugmented unipolar leads is more complicated. The difference between the nonaugmented and augmented leads lies in the addition of another branch from the "indifferent" terminal to the limb being studied. This extra branch, like the others, includes a fixed, inserted resistance as well as the variable electrode skin resistance.

The effect of imbalance of the skin resistances at the other two branches is to produce changes similar in nature to those described for the aV leads. For

example, in recording Lead V_F, if the right arm skin resistance is very high, but the resistances at the other electrodes are low and equal, V_F would have the configuration of Lead III but only one-half its amplitude. Fig. 2 is a diagram illustrating this point.

Another and different effect can occur in the nonaugmented leads due to skin resistance variations at the skin contact of the extra branch leading from the "indifferent" terminal to the limb being explored. For example, again in V_F, if the skin resistances at the arms are equal but that of the branch electrode at the leg is very high, the potential of the "indifferent" electrode will be the average of the arms alone. In that instance, aV_F rather than V_F will be recorded.

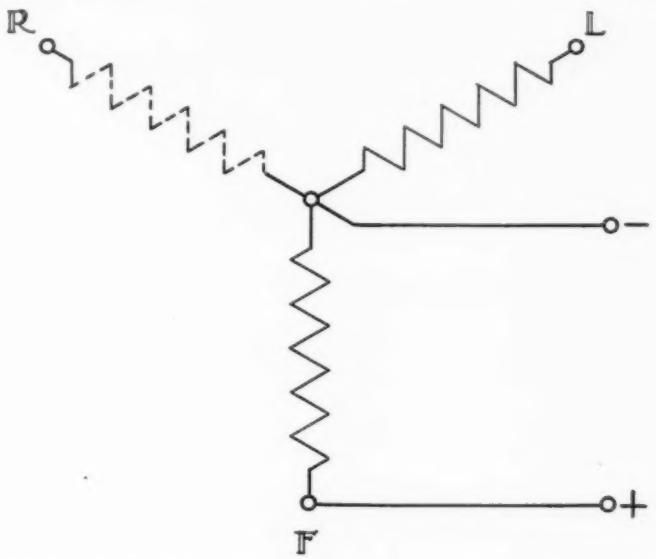

Fig. 2.—Connections for Lead V_F. The dotted line indicates high resistance at the right arm, so that the potential at the "indifferent" terminal is midway between that of L and F. Expressed algebraically, the actual recorded potential at F equals $F - \frac{(F + L)}{2}$, or ½ Lead III.

On the other hand, if the resistance at the branch electrode contact at the leg is very low in comparison to those at the arms, the potential at the "indifferent" electrode does not represent the true average of its three contributing limbs. Since the contribution from the leg meets with less resistance than that from the other limbs, the potential at the "indifferent" terminal will be shifted towards that of the leg. Thus, the difference in potential between the exploring electrode and this central terminal becomes less, and the amplitude of the recorded Lead V_F becomes smaller, although its shape does not change.

Alterations of skin resistance at the exploring electrode of either augmented or nonaugmented unipolar leads has little effect. This skin resistance can be considered as part of the resistance of the recording apparatus itself, at least 100,000 ohms in the case of electronic electrocardiographs. Quantitative considerations concerning the effect of skin resistance on unipolar leads are detailed

in the Appendix. The simple examples given above indicate qualitatively that variations in skin resistance affect the amplitude of the nonaugmented extremity leads. This probably explains many of the variations in the relationship between augmented and nonaugmented leads described by Simonson and Keys.[1]

Similar considerations, of course, must apply to the unipolar precordial leads. However, the precordial voltages are so large that ordinarily alterations in extremity skin resistance do not lead to appreciable clinical error in these leads.

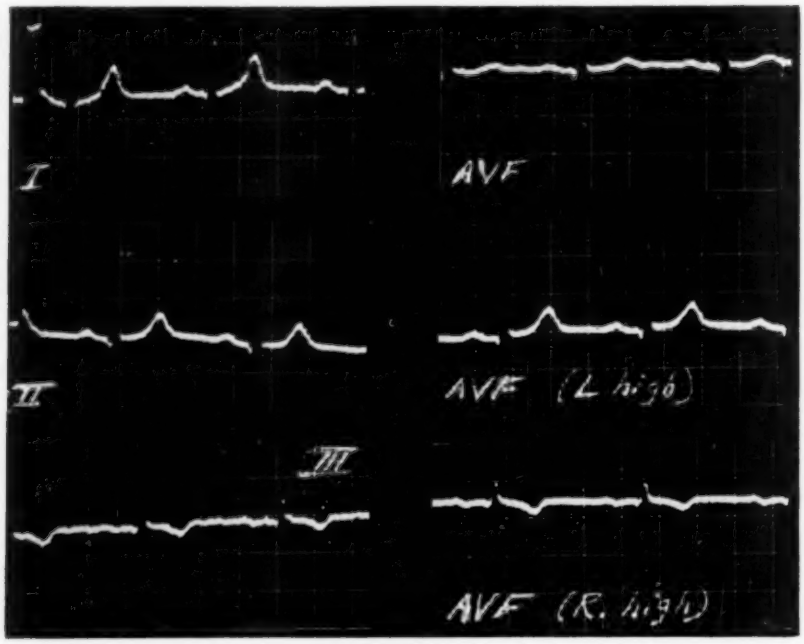

Fig. 3.—Changes in Lead aV_F produced by altering the skin resistance at the arms.

PROCEDURE

In order to demonstrate the effect of dissimilar skin resistances on the electrocardiogram, we deliberately unbalanced the skin resistances in the extremities contributing to the "indifferent" electrode. For example, in studying the effect on Lead aV_F, we rubbed in the electrode paste at the right arm electrode but applied it without rubbing at the left arm. Then we reversed the procedure, rubbing the paste in well at the left arm connection and applying it without rubbing at the right arm. Finally, a tracing was taken with the paste rubbed in well at both left and right arms.

Examples of Distortion Caused by Unbalanced Skin Resistance.—Fig. 3 illustrates errors in recording QRS and T complexes in Lead aV_F, deliberately introduced by altering skin resistance in the left and right arms, successively. The standard leads reveal an upright T in Lead II and an inverted T in Lead III. When Lead aV_F is recorded with low-skin resistance at both arms, the QRS is four mm. tall and the T wave one to two mm. tall. With unbalanced resistances (left-

arm resistance high and right-arm resistance low), the recorded "aV_F" presents a ten mm.-tall QRS and a three-to-four mm. tall T wave. The similarity to standard Lead II is apparent. On the other hand, with the resistances unbalanced in the reverse order (right arm high and left arm low), the recorded "aV_F" presents a two-to-three mm. tall QRS and a sharply inverted T wave. Here the resemblance of the recorded "aV_F" to standard Lead III is striking.

Fig. 4 illustrates errors in recording Lead aV_L which were deliberately introduced by altering skin resistances in the "indifferent" electrode. In the standard leads, QRS is biphasic in Lead I, upright in Leads II and III. T is upright in all three standard leads, being tallest in Lead II. When aV_L is recorded with balanced resistances in the right arm and left leg, a biphasic but predominantly negative QRS and a low isoelectric T wave are seen. Observe the biphasic P wave. When the resistances are unbalanced (left leg high, right arm low), the resulting "aV_L" strongly resembles standard Lead I. The QRS is less negative, T distinctly positive, and the P wave also has become upright. When the skin resistances were reversed (right arm high and left leg low), all electrical complexes of the recorded "aV_L" became negative, as in standard Lead III inverted.

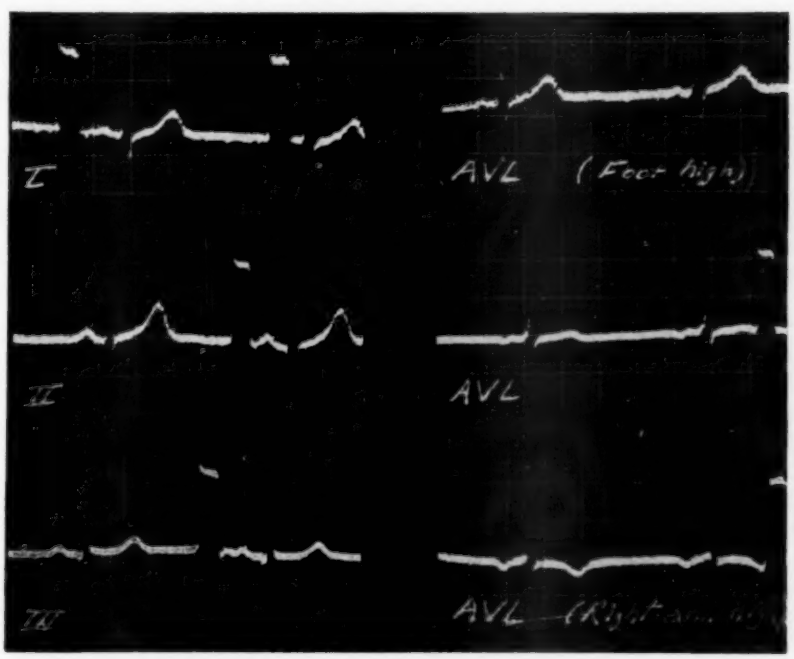

Fig. 4.—Changes in Lead aV_L produced by altering the skin resistance at the left foot and the right arm, successively.

Figs. 3 and 4 illustrate errors deliberately introduced into the electrocardiogram. Fig. 5 illustrates an error produced unintentionally in clinical practice. The tracing submitted for interpretation included an inverted T in Lead aV_F. It was clear, however, that since the sum of the T waves in the three unipolar

leads was not zero, a technical error had occurred. The strong resemblance of the originally recorded "aV_F" to Lead III, and that of the original "aV_L" to inverted Lead III suggested that faulty preparation of the skin at the right arm was the cause of the difficulty. When the tracing was repeated, with special attention to proper skin preparation, T in Lead aV_F was upright and the configuration of Lead aV_L changed appropriately.

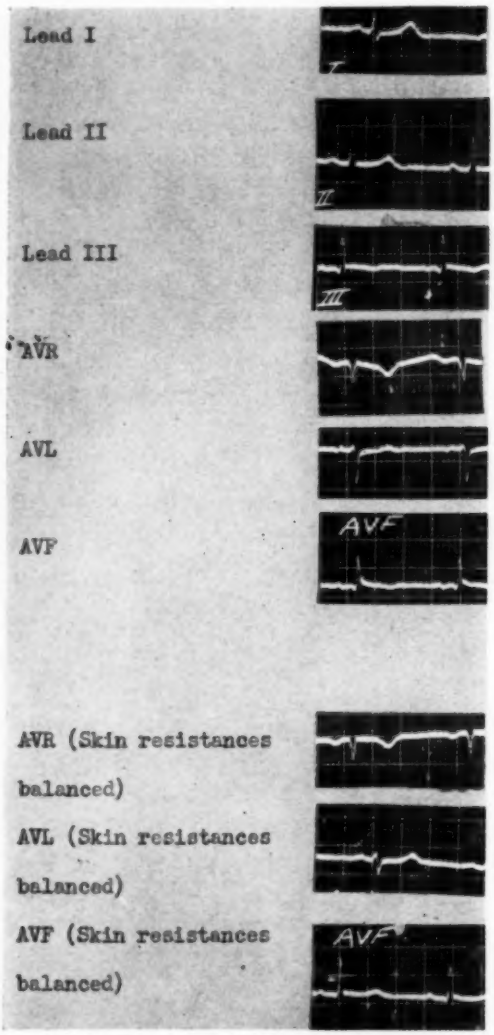

Figure 5.—Above, the electrocardiogram submitted for interpretation and showing inverted T_{AVF}. Below, the unipolar leads retaken with balanced skin resistances. T_{AVF} is upright.

Detection of errors of this type is extremely important, particularly when serial tracings are being taken to evaluate suspected acute myocardial changes, as in infarction or pericarditis. In such instances, "serial changes" in the unipolar leads may be taken as evidence of disease, when in fact they reflect only a tech-

nical error. Indeed, electrocardiograms containing errors of this nature have been reproduced in textbooks and articles concerned with cardiology. Quick recognition of these errors is possible if the rule "aV_R plus aV_L plus aV_F equals zero" is applied. In a given tracing, once the presence of error has been determined by application of the rule, the specific site of the high-skin resistance can be worked out.

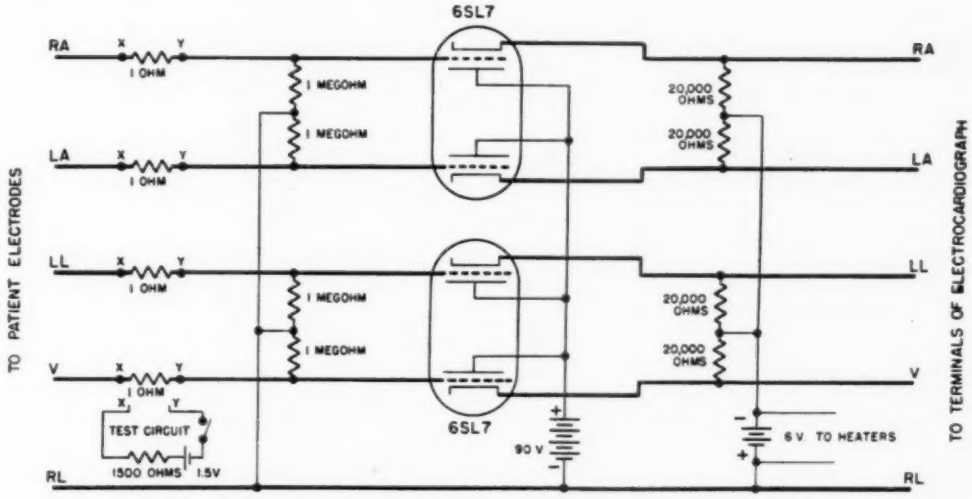

Fig. 6.—Circuit of coupling device for eliminating distortion. With the tubes and the values of the components as selected, the transmission loss through this device is negligible. The voltages applied to the input terminals of the electrocardiograph are practically exactly the same as the voltages of the patient's electrodes, over a wide variation of tube characteristics, voltages, and the values of resistors. In order to test the apparatus, a test circuit is provided as indicated, which can be connected to the one-ohm resistance in any one of the input leads, impressing a voltage of one millivolt. The impedance looked at from the output is very low (in the order of a few hundred ohms), so that variations due to differences in tubes or resistors will have no effect. It is assumed that the usual circuits for obtaining unipolar leads are incorporated in the electrocardiograph, and the test circuit must always be applied to an appropriate lead: for example, in Lead I it must be applied to either left arm or right arm, in Lead aV_R to the right arm, etc.

Methods for Eliminating Errors Due to Unbalanced Resistances.—The most obvious approach to the elimination of errors due to unbalanced skin resistances is, of course, accurate matching of resistances prior to recording the electrocardiogram. Goldberger[2] has described two possible techniques, one using a string galvanometer, the other involving a trial-and-error method with variable resistances. Both of these methods require first the measurement of the skin resistance and then a balancing procedure.

Needle electrodes, which match resistances very well by completely bypassing the skin, provide another solution. Although acceptable theoretically, and perhaps even useful for experimental work, this method is unacceptable clinically.

An electronic coupling device which will be described eliminates effectively the errors caused by unbalanced skin resistance. With electronic amplifier electrocardiographs, the effect of skin resistance on the standard leads has been made negligible by introducing very high input resistance, so that wide variation in

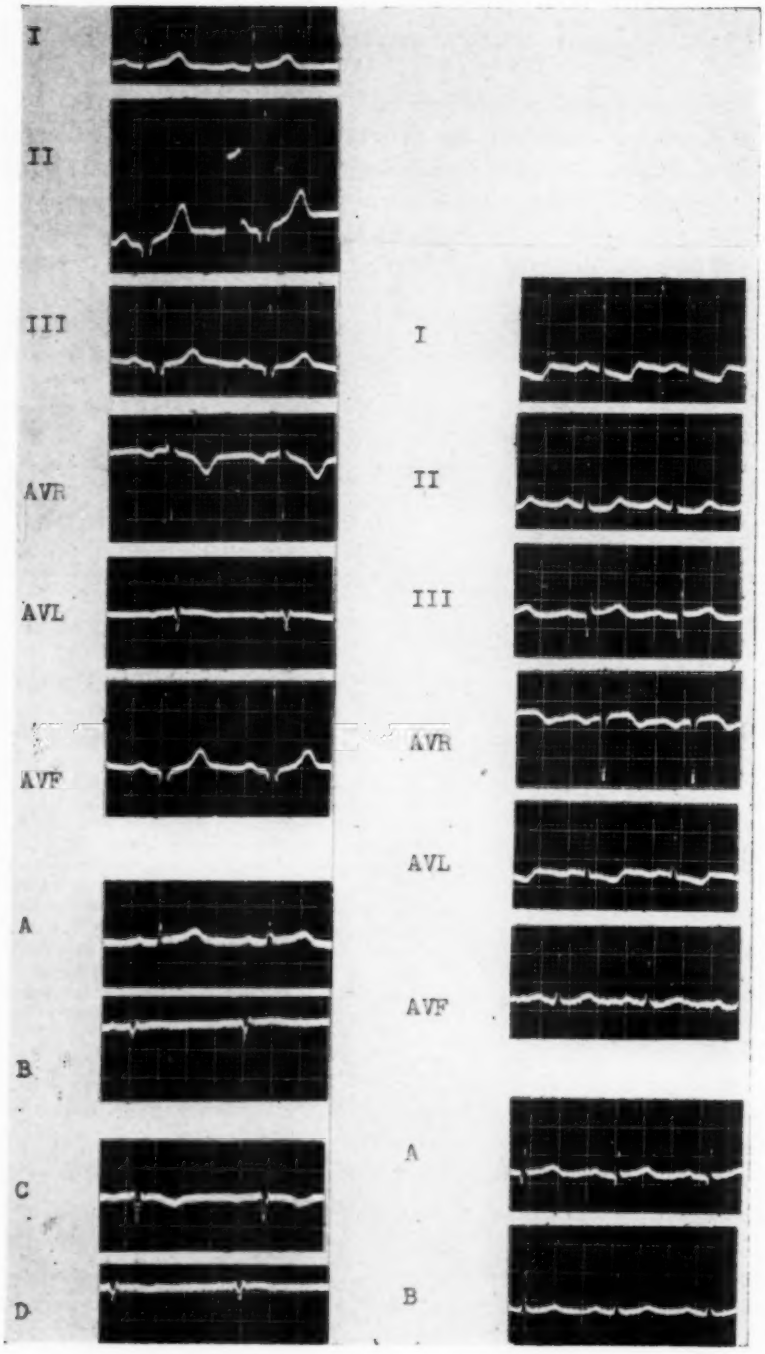

Fig. 7 Fig. 8

Fig. 7.—Prevention of errors by use of the electronic device. The electrocardiogram in the upper six records recorded with all resistances low. *A* is aV_L recorded with high resistance at the foot; *B* is the same except for the use of the electronic device; *C* is aV_L recorded with resistance high at the right arm; *D* is the same except for the use of the device. Note the similarity of *B* and *D* to aV_L, and the marked changes in *A* and *C* produced by high-skin resistance.

Fig. 8.—Prevention of errors by use of the electronic device. The electrocardiogram in the upper six records was recorded with all resistances low. Note the absence of Q_{AVF}. *A* is aV_F recorded with high resistance at the right arm; note the appearance of Q_{AVF}. *B* is the same as *A* except for the use of the electronic device. Note the elimination of the erroneous Q_{AVF}.

skin resistance becomes inconsequential. The same principle can be applied to the unipolar leads, except that the high input resistance must be between the electrodes and the point in the lead network to which the electrode would be attached. One of us (MMS) has designed such an apparatus, a diagram of which is shown in Fig. 6. The electron tubes which are connected to the patient are used as cathode followers, so that the potentials of the cathodes follow practically the same course as the potentials of the grids which are connected to the electrodes. The cathodes are connected to the usual recording systems for recording any desired lead.

Figs. 7 and 8 illustrate that this device prevents errors which would otherwise be recorded in the presence of unbalanced skin resistances.

Fig. 7 shows the usual standard and augmented unipolar leads, taken with low-skin resistance throughout. The resistance was then made high at the left leg, and "aV_L" again recorded (record *A*). The change in P, QRS, and T results in a tracing strongly resembling standard Lead I. Without changing the skin resistance, Lead aV_L was again recorded, but this time the electronic coupling device was used. This tracing (*B*) is identical with Lead aV_L as recorded with low resistance. In *C*, Lead "aV_L" was recorded without the electronic device and with high resistance in the right arm. The resulting tracing resembles Lead III inverted and is grossly different from the record with low resistances. At this point, the electronic coupling device was again used. The tracing obtained (*D*) is a record free of the errors seen in *C*, being identical with aV_L as taken with low resistances.

Fig. 8 illustrates the prevention of a false Q in Lead aV_F. The standard and augmented unipolar leads were first recorded with low resistance throughout. No Q was present in Lead aV_F. In *A*, high resistance was produced at the right arm and Lead aV_F changed, so that the initial QRS deflection became negative, a Q wave. The electronic coupling device was then used and the tracing retaken without changing the skin resistances. The resulting record *B* is identical with that seen with low resistances at all contact points.

DISCUSSION

Quantitative expressions for the distortion due to unbalanced resistances have been given by Rappaport and associates,[3] and by Bryant and associates.[4] However, a very simple relationship seems to have been overlooked. It may be shown that the effect of imbalance, except for minor effects on amplitude, is to change the angle of projection which represents the lead being recorded. Lead aV_R, as is well known, is a recording of a projection on a line extending to the right, 30 degrees above the horizontal. The axis of Lead aV_L extends to the left 30 degrees above the horizontal, and that of Lead aV_F is directed vertically downwards.

The effect of unbalanced resistors in recording unipolar limb potentials is to shift the line of projection, or the axis, a maximum of 30 degrees to either side of the correct direction.

The degree of shift depends on the degree of relative imbalance. For example, Lead aV_F would record as standard Lead II (30 degrees counterclockwise from Lead aV_F) if the left-arm resistance were infinite compared to the right-arm resistance. On the other hand, if the right-arm resistance were infinite in comparison to the left-arm resistance, a 30-degree clockwise shift in the axis of aV_F would occur, and standard Lead III would be recorded. Any actual ratio of the two arm resistances results in a shift in the axis of Lead aV_F somewhere between these extremes. Thus, since the actual axis of the lead is changed, alterations in configuration, not only in amplitude, result. As has been shown, these changes may be so striking as to alter the actual direction of P, QRS, or T deflections. Naturally, if the axis of a unipolar lead is perpendicular to a given deflection, the tracing with resistances balanced is isoelectric. In such cases, even a small shift in the axis of the lead in question may result in a large change in configuration, as any shift at all must necessarily result in a change in direction of the complex. Such an instance was illustrated in Fig. 4. Here, in Lead aV_L with balanced resistances, P, QRS, and T were all of small magnitude or isoelectric. In other words, the axis of Lead aV_L was approximately perpendicular to all of these complexes. Any alteration in skin resistances at the right arm or left leg changes the position of the axis of Lead aV_L, and therefore major changes in all deflections result.

Artifactual production of a Q wave in Lead aV_L or Lead aV_F deserves special mention, as the appearance of such waves is of clinical significance. As has been pointed out, high resistance at the right arm results in a shift of the axis of aV_L towards negative Lead III. In a case with an initial portion of QRS really isoelectric in aV_L, this initial portion could be recorded as a negative deflection, of Q wave. Similar considerations apply to Lead aV_F. For example, if the initial portion of QRS is really isoelectric in aV_F, aV_F with resistances balanced cannot record this portion as a Q. However, if the resistance at the right arm becomes high, the axis of aV_F shifts towards the axis of Lead III, in which position a Q in Lead "aV_F" could be recorded.

Without the apparatus described, errors due to unbalanced skin resistances generally can be prevented if care is taken to rub the electrode paste in well at all contact points. In occasional cases this measure will not suffice and errors will appear. As explained above, these errors should be detected as part of routine electrocardiographic interpretation. The inclusion of this electronic device in electrocardiographs would eliminate errors in unipolar limb leads and make them more reliable.

SUMMARY

1. Unbalanced or dissimilar skin resistances may seriously alter deflections in the unipolar limb leads and lead to important clinical errors. These changes are due to potential variations at the so-called "indifferent" electrode and may occur in either augmented or nonaugmented unipolar extremity leads.

2. Changes in amplitude, contour, and direction of P, QRS, and T waves were produced experimentally by altering skin resistances. These changes included the inversion of normally upright T waves and the production of Q waves not present with resistances balanced.

3. These errors result from an inadvertent shift in axis of the unipolar leads clockwise or counterclockwise to a maximum of 30 degrees. The amount of shift in axis depends on the degree of imbalance. Thus, aV_R (or V_R) may then erroneously resemble Lead I inverted or Lead II inverted; aV_L (or V_L) may resemble Lead I or Lead III inverted; and aV_F (or V_F) may resemble Lead II or Lead III.

4. An electronic coupling device is described which prevents errors in unipolar limb leads due to dissimilar skin resistances even when the imbalance is extreme.

APPENDIX

The quantitative effects of imbalance may be derived by consideration of its effects upon the potential of the "indifferent" point. In the connection for the V leads, the "indifferent" point is connected by conducting paths to each of the three limbs. The resistance of each path is composed of the fixed inserted resistance and the skin resistance at the electrode; the conductance of each path is the reciprocal of this total resistance. If the conductance to the three limbs is designated by σ_R, σ_L, and σ_F, it may be shown by application of Kirchoff's laws of electrical circuits that the potential of the "indifferent" point, X_V, is given by:

$$X_V = \frac{R\sigma_R + L\sigma_L + F\sigma_F}{\sigma_R + \sigma_L + \sigma_F} \tag{1}$$

where R, L, and F are the potentials of the three limbs. In the derivation of Equation (1) it is assumed that the potentials of the limbs are unaffected by the connection of the resistances. This is not strictly correct but is practically so because the internal resistance of the body is very much smaller than the skin resistances and the added resistances in the circuit.

The potential of the "indifferent" point for the aV leads is different for each lead and is derivable from X_V by setting the appropriate σ in each case equal to zero. Thus, for aV_R the corresponding X_{AVR} is found from the value of X_V by setting $\sigma_R = 0$ since in this connection the branch to the right arm is not connected, so that the resistance of that branch is infinite, or the conductance zero. We have:

$$X_{AVR} = \frac{L\sigma_L + F\sigma_F}{\sigma_L + \sigma_F}$$

$$X_{AVL} = \frac{R\sigma_R + F\sigma_F}{\sigma_R + \sigma_F} \tag{2}$$

$$X_{AVF} = \frac{R\sigma_R + L\sigma_L}{\sigma_R + \sigma_L}.$$

When the resistances are all balanced, all the σ's concerned are equal. The values of the potentials of the "indifferent" point under such circumstances are the ideal values and will be designated by the subscript 0. We have, from Equations (1) and (2):

$$X_{V0} = \frac{R + L + F}{3} \tag{3}$$

and

$$X_{AVR0} = \frac{L + F}{2}, \quad X_{AVL0} = \frac{R + F}{2}, \quad X_{AVF0} = \frac{R + L}{2} \tag{4}$$

he true values of the V and AV leads are recorded if the resistances are balanced, i.e., if all the σ's concerned are equal. We denote these also by the subscript 0. They are given by:

$$V_{R0} = R - X_{V0} = R - \frac{R + L + F}{3} = -\frac{L - R}{3} - \frac{F - R}{3} = -\frac{I + II}{3}$$

$$\text{similarly,} \quad V_{L0} = \frac{I - III}{3} \tag{5}$$

$$\text{and} \quad V_{F0} = \frac{II + III}{3}$$

also:

$$aV_{R0} = R - X_{AVR0} = R - \frac{L + F}{2} = -\frac{L - R}{2} - \frac{F - R}{2} = -\frac{I + II}{2}$$

$$\text{similarly,} \quad aV_{L0} = \frac{I - III}{2} \tag{6}$$

$$\text{and} \quad aV_{F0} = \frac{II + III}{2}$$

These relations are well known but are often derived with the help of the inexact biophysical assumption that $R + L + F = 0$. This assumption is not required and is not used in the derivation here given.

A similar procedure may be carried through for the general unbalanced case. We obtain.

$$V_R = R - X_V = -\frac{I\sigma_L + II\sigma_F}{\sigma_R + \sigma_L + \sigma_F}$$

$$\text{similarly,} \quad V_L = \frac{I\sigma_R - III\sigma_F}{\sigma_R + \sigma_L + \sigma_F} \text{ and } V_F = \frac{II\sigma_R + III\sigma_L}{\sigma_R + \sigma_L + \sigma_F} \tag{7}$$

also:

$$aV_R = R - X_{AVR} = -\frac{I\sigma_L + II\sigma_F}{\sigma_L + \sigma_F}$$

$$\text{similarly,} \quad aV_L = \frac{I\sigma_R - III\sigma_F}{\sigma_R + \sigma_F} \text{ and } aV_F = \frac{II\sigma_R + III\sigma_L}{\sigma_R + \sigma_L}. \tag{8}$$

From Equations (7) and (8) the various limiting cases discussed in the body of this article follow directly. For example, in the case of aV_L, if the left leg resistance is very high compared to that of the right arm, $\sigma_F = 0$ and $aV_L = I$; in the case of V_F, if the left arm resistance is high compared to that of the right arm and left leg, both of which are equal, $\sigma_L = 0$ and $\sigma_R = \sigma_F$, so that $V_F = II/2$.

Furthermore, by comparison of Equation (7) and (8), we have

$$\frac{aV_R}{V_R} = \frac{\sigma_R + \sigma_L + \sigma_F}{\sigma_L + \sigma_F}$$

$$\frac{aV_L}{V_L} = \frac{\sigma_R + \sigma_L + \sigma_F}{\sigma_R + \sigma_F} \tag{9}$$

$$\frac{aV_F}{V_F} = \frac{\sigma_R + \sigma_L + \sigma_F}{\sigma_R + \sigma_L}$$

These relations show that the ratio of any aV to the corresponding V lead is a simple number being independent of the voltages. The form of the augmented and unaugmented unipolar

leads are thus the same, the amplitudes being proportional,* if the resistances which are common to the two methods are the same.

The relations Equations (7) and (8) are not in a form suited to the vectorial representation of the effect of imbalance. Relations better adapted for this point of view may be derived by considering the shift in potential of the "indifferent" point resulting from imbalance. We need to investigate only the aV cases because, as we have seen from Equations (9), the V leads are merely proportional to them. The shift in potential is the difference between the values given by Equations (4) and those given by Equations (2). These differences are as follows:

$$X_{AVR_0} - X_{AVR} = \frac{L + F}{2} - \frac{L\sigma_L + F\sigma_F}{\sigma_L + \sigma_F} = (F - L)\frac{\sigma_L - \sigma_F}{2(\sigma_L + \sigma_F)} = III\frac{\sigma_L - \sigma_F}{2(\sigma_L + \sigma_F)}$$

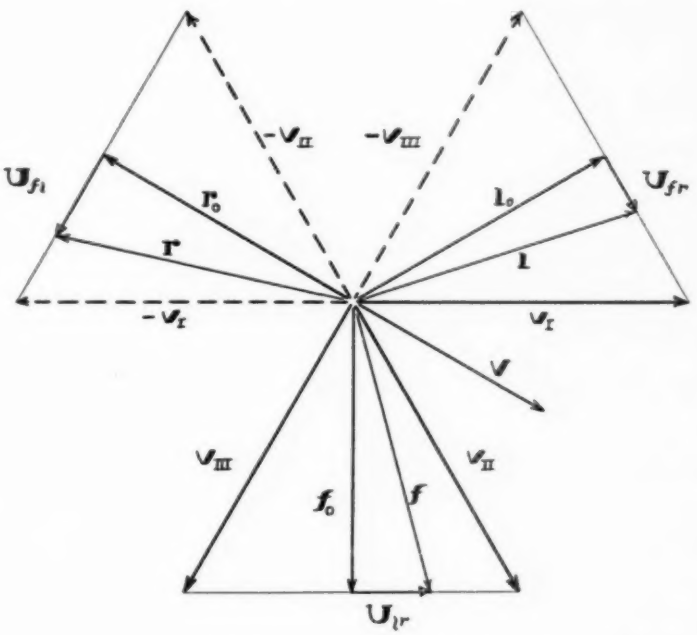

Fig. 9.—Diagram to show effect of imbalance on vector axes. **V** is the vector representing the manifest potential. $\mathbf{V}_I$, $\mathbf{V}_{II}$, and $\mathbf{V}_{III}$ are unit vectors representing the axes of the standard leads. $\mathbf{r}_0$, $\mathbf{l}_0$, and $\mathbf{f}_0$ are the vector axes of the unipolar leads. It is obvious that $\mathbf{r}_0 = -\frac{\mathbf{V}_I + \mathbf{V}_{II}}{2}$; $\mathbf{l}_0 = \frac{\mathbf{V}_I - \mathbf{V}_{III}}{2}$; and $\mathbf{f}_0 = \frac{\mathbf{V}_{II} + \mathbf{V}_{III}}{2}$. **r**, **l**, and **f** are the vector axes of the unipolar leads with imbalance. The imbalance has the effect of shifting the unipolar axes so that $\mathbf{r} = \mathbf{r}_0 + \mathbf{U}_{fl}$; $\mathbf{l} = \mathbf{l}_0 + \mathbf{U}_{fr}$; and $\mathbf{f} = \mathbf{f}_0 + \mathbf{U}_{lr}$. $\mathbf{U}_{fl}$ and $\mathbf{U}_{fr}$ and $\mathbf{U}_{lr}$ are the three imbalance vectors given by:

$$\mathbf{U}_{fl} = \mathbf{V}_{III}\frac{\sigma_L - \sigma_F}{2(\sigma_L + \sigma_F)};\quad \mathbf{U}_{fr} = \mathbf{V}_{II}\frac{\sigma_R - \sigma_F}{2(\sigma_R + \sigma_F)};\quad \mathbf{U}_{lr} = \mathbf{V}_I\frac{\sigma_R - \sigma_L}{2(\sigma_R + \sigma_L)}.$$

*All the relationships stated herein in quantitative form are also correct if, besides resistance, the skin contacts display the phenomenon of polarization. Under such circumstances, the σ's would not be conductances but complex admittances. In such a case, the ratios of aV to V are not, in general, real numbers, so that the conclusion drawn from Equations (9) would not be correct. Similar remarks hold for the vectorial representation. If the σ's are not real, the effects would depend on the form of the waves themselves, so that the simple vector interpretations made below would not be correct. In this work, we have not found such polarization effects to be of any significance.

similarly,

$$X_{AVL_0} - X_{AVL} = II \frac{\sigma_R - \sigma_F}{2(\sigma_R + \sigma_F)} \qquad (10)$$

$$\text{and } X_{AVF_0} - X_{AVF} = I \frac{\sigma_R - \sigma_L}{2(\sigma_R + \sigma_L)}.$$

The aV leads as recorded differ from the true values by just these shifts. Thus, from Equations (10):

$$aV_R = aV_{R_0} + III \frac{\sigma_L - \sigma_F}{2(\sigma_L + \sigma_F)}$$

$$aV_L = aV_{L_0} + II \frac{\sigma_R - \sigma_F}{2(\sigma_R + \sigma_F)} \qquad (11)$$

$$aV_F = aV_{F_0} + I \frac{\sigma_R - \sigma_L}{2(\sigma_R + \sigma_L)}.$$

In the vectorial representation, the manifest potential vector **V** is defined as the vector of the projections of which at any instant on the three axes $\mathbf{V}_I$, $\mathbf{V}_{II}$, and $\mathbf{V}_{III}$ are, respectively, the values of Leads I, II, and III at that instant. In this representation, the vectors $\mathbf{r}_0$, $\mathbf{l}_0$, and $\mathbf{f}_0$ are the axes of the unipolar (augmented) leads and are, respectively, given by analogy with Equations (6) by

$$\mathbf{r}_0 = -\frac{\mathbf{V}_I + \mathbf{V}_{II}}{2}, \quad \mathbf{l}_0 = \frac{\mathbf{V}_I - \mathbf{V}_{III}}{2} \text{ and } \mathbf{f}_0 = \frac{\mathbf{V}_{II} + \mathbf{V}_{III}}{2}.$$

The axial vectors $\mathbf{V}_I$, $\mathbf{V}_{II}$, and $\mathbf{V}_{III}$ are usually considered to be unit vectors, so that $\mathbf{r}_0$, $\mathbf{l}_0$, and $\mathbf{f}_0$ are not of unit length, but have the length $\sqrt{3}/2$ (See Fig. 9). Thus, the three augmented unipolar leads are given by the projection of the manifest potential vector on $\mathbf{r}_0$, $\mathbf{l}_0$, and $\mathbf{f}_0$, each multiplied by $\sqrt{3}/2$.

From Equations (11), it may be seen that the axis of the actually recorded unipolar augmented lead is the sum of the unipolar axis vector and an "imbalance" vector, in the direction parallel to a standard axis, but of magnitude given by one-half the ratio of the difference to the sum of the conductances in the branches. These vectors **r, l,** and **f** are shown in the figure. It is clear that they may vary in direction over a range of 30 degrees to each side of the unipolar axis and that their magnitude varies between $\sqrt{3}/2$ and unity.

From Equations (9), it follows that the nonaugmented unipolar leads are projections of the manifest potential vector on the same axes **r, l,** and **f.** The magnitudes must, however, be multiplied not only by the lengths of these vectors, but also by the factors given by Equations (9).

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THE POTENTIAL DISTRIBUTION ON THE BODY SURFACE CAUSED BY A HEART VECTOR

Calculations on Some Simple Models

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I. INTRODUCTION

THE electrical action of the heart may be described to a certain approximation by one single vector, the heart vector. The classical equilateral triangle of Einthoven and associates[1] provided a means of finding this vector from the extremity leads. The true relation between the heart vector and leads, however, is a more complicated one. As has been pointed out previously,[2,4] the potential difference V_{PQ} between two electrodes P and Q is a linear function of the components X, Y, Z of the heart vector

$$V_{PQ} = aX + bY + cZ \ . \qquad (1)$$

The coefficients a, b, c remain constant during the heart beat and depend on the shape and conductive properties of the trunk. They can be determined on a phantom or on dead human bodies. But apart from this experimental method, it may be useful to treat the problem mathematically. This can only be done, however, by making some very simplifying assumptions. If the trunk is treated as a homogeneous sphere with the heart vector (dipole) acting in its center, the solution can be readily given and is a three dimensional generalization of the Einthoven triangle. If the position of the heart is not central, however, a more complicated mathematical treatment is required. Wilson and Bayley[5] have treated this case, and they have given explicit formulas for the potential distribution.

The shape of the human trunk, however, is more like a cylinder than like a sphere. It was thought desirable, therefore, to calculate the potential distribution on a cylinder generated by a dipole. To avoid too complicated calculations, the cylinder is chosen circular, and the dipole is placed on its axis. Furthermore, it is assumed to be homogeneous, since a theoretical treatment of the conduction in a heterogeneous cylinder seems to be hardly possible. The shape of the cylinder is seen from Fig. 1. The ratio of the radius to the height, as well as the position of the dipole (heart), can be chosen arbitrarily. However, since a numerical calculation is required and the result cannot be given in explicit formulas, we had to decide upon these ratios. We have chosen a cylinder with radius R and the upper and lower boundary plane at $z = -1.5$ and $z = 2.2$ R, respectively. (The position of the dipole, the heart, is chosen as the origin.)

The closed cylinder may be a fairly good approximation of the actual case. However, the body is flattened and the heart is eccentrically placed. To give a

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qualitative discussion of differences in the shape of the model on the potential distribution, we also discuss the potential distribution on the open (infinite) cylinder, and on two parallel planes, caused by a dipole.

II. GEOMETRICAL REPRESENTATION BY MEANS OF AN IMAGE SURFACE

In a previous paper[4] one of us, in collaboration with J. B. van Milaan, developed a geometrical representation of the relation between the heart vector and leads, the boundary of the trunk, and its heterogeneity being quite arbitrary. This representation can be deduced from Equation (1), in which X, Y, Z are components of a vector, the heart vector, and V_{PQ} is a potential difference and therefore a scalar quantity. It can be shown from this that the coefficients $\overrightarrow{a, b, c}$ must have the character of vector components. So there is a vector a, b, c. The relation, Equation (1), can be interpreted geometrically: the potential difference V_{PQ} equals the projection of the heart vector $\overrightarrow{X, Y, Z}$ on the vector $\overrightarrow{a, b, c}$ times the length of the latter. It is the so-called scalar product of both vectors.

We take for Q a fixed point on the body surface. Then to each point P on this surface a vector $\overrightarrow{a, b, c}$ corresponds according to Equation (1). This vector may be drawn from a fixed origin. The terminus P′ of this vector can be considered as an image of the point P. To each point P of the body belongs a point P′ in the image space. The locus of all points P′ is the image of the real body surface. The potential distribution on the real body surface can be deduced from the image surface, if the correspondence of the points P and P′ everywhere on the surface is known, and so for any arbitrary direction of the heart vector. To find the potential difference of two points P and Q we have only to find the corresponding points P′ and Q′ on the image surface and to project the heart vector on the line P′Q′. The product of the projection and the length of P′Q′ is equal to the potential difference between P and Q.

In the following sections we shall calculate the image surface for some mathematically single cases (body surface is an open cylinder, a closed cylinder, and two parallel planes, respectively). By some examples we shall show how the image surface can be used.

III. THE POTENTIAL DISTRIBUTION ON AN OPEN (INFINITE) CYLINDER

The dipole can be decomposed into two components, one along the axis of the cylinder and the other perpendicular to it. We calculate the field separately for both cases and calculate the field in an open infinite cylinder (without boundaries at the top and at the bottom).

We shall use cylindrical coordinates r, ϑ, z; their relation to the Cartesian coordinates, x, y, z is shown in Fig. 1. Inside the cylinder the potential φ (r, ϑ, z) is a function of the cylindrical coordinates r, ϑ, z (or of the rectangular coordinates x, y, z). This function obeys a differential equation, expressing that there is no electric charge inside the cylinder. In rectangular coordinates this equation has the simple form:

$$\frac{\partial^2\varphi}{\partial x^2} + \frac{\partial^2\varphi}{\partial y^2} + \frac{\partial^2\varphi}{\partial z^2} = 0, \text{ or abbreviated } \Delta\varphi = 0.$$

The way in which this is expressed in the cylindrical coordinates r, ϑ, z can be found in Appendix I.

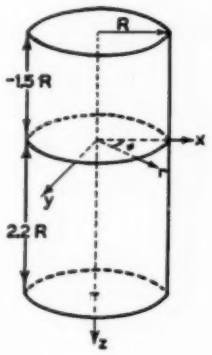

Fig. 1.

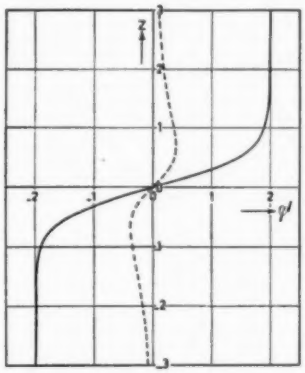

Fig. 2.

Fig. 1.—Shape of the cylinder for which the potential distribution is calculated. The position of the dipole (the heart) is taken as the origin of the coordinate system. The relations between the Cartesian coordinates (*x*, *y*, *z*) and the cylindrical coordinates (*r*, ϑ, *z*) are also shown.

Fig. 2.—The potential $\varphi''(R, z)$, caused by a dipole parallel to the axis of the infinite cylinder on its surface, as a function of z. The dotted line shows the potential at the same places, if the entire space is filled with the conducting medium.

At the origin, where the dipole is assumed to be acting, φ must become infinite and no longer satisfies $\Delta\varphi = 0$. We require that φ obey the following expression near the origin:

$$\varphi\left(\vec{\rho}\right) = \vec{p}\cos\gamma/\rho^2 \tag{2}$$

($\vec{p}$ is the dipole moment and $\vec{\rho}$ the radius vector, γ is the angle between the vectors $\vec{p}$ and $\vec{\rho}$). At the surface of the "trunk," i.e., at the cylindrical surface, the normal component of the current density is zero, thus $\frac{\partial\varphi}{\partial n} = 0$ (n being the direction normal to the surface).

In Appendix I the general mathematical treatment is given. In Appendix II the calculations are carried out for a dipole parallel to the axis of an infinite cylinder. The potential does not depend on ϑ since rotational symmetry exists and we can write φ'' (r,z). The results for the surface of the cylinder and for a dipole of unit moment are given in Fig. 2. (For comparison, we have also drawn the potential which would be caused by the same dipole in infinite space at the same places.)

In Appendix III the formulas are given for the potential of a unit dipole perpendicular to the axis of an infinite cylinder. If the dipole is directed along the x-axis, we shall denote the potential by $\varphi^*(r, \vartheta, z)$. It appears to be the product of a function $F^*(r,z)$ of r and z only and $\cos\vartheta$, so on the surface of the cylinder:

$$\varphi^*(r, \vartheta, z) = F^*(z)\cos\vartheta\ . \tag{3}$$

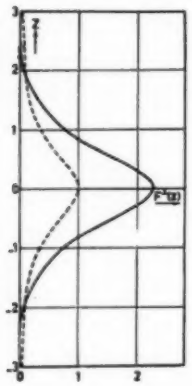

Fig. 3.—The potential F^* (z), caused by a dipole in the x-direction perpendicular to the axis of the infinite cylinder, on the generating line x = 0, y = 1 of its surface, as a function of z. The dotted line shows the potential at the same places if the entire space is filled with the conducting medium.

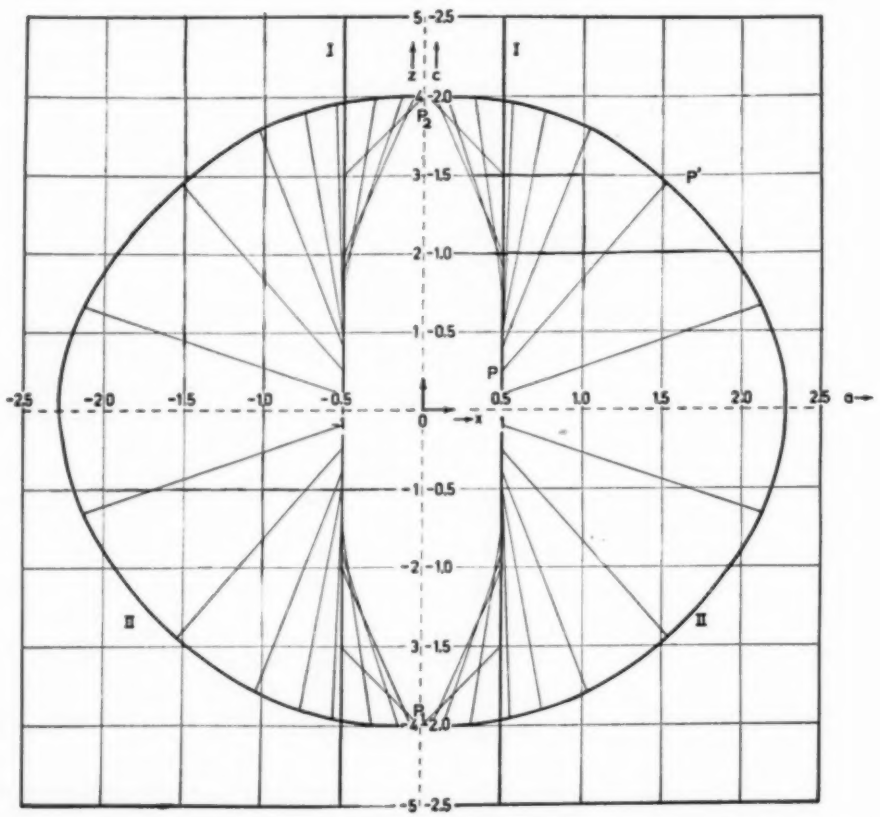

Fig. 4.—The image surface of an infinite cylinder. The correspondence between a point P of the cylinder and P' of the image surface is indicated by a straight line. *I*, Intersection of the cylinder with the x-z plane. *II*, Intersection of the image surface with the a-c plane.

The function $F^{\wedge}(z)$ is represented in Fig. 3 (again the potential of the same dipole in infinite space is drawn for comparison).

We now give the results for the potential distribution by means of an image surface. If X, Y, Z are the components of the heart vector, the potential φ can be composed of contributions from each of these components. Z, parallel to the axis of the cylinder gives:

$$\varphi_z = Z\varphi''(r, z) .$$

X and Y, perpendicular to the axis of the cylinder give:

$$\begin{aligned} \varphi_x &= X\varphi^{\wedge}(r, \vartheta, z) = XF^{\wedge}(z) \cos \vartheta \\ \varphi_y &= YF^{\wedge}(z) \sin \vartheta . \end{aligned}$$

So the total value of the potential is:

$$\varphi = \varphi_x + \varphi_y + \varphi_z = XF^{\wedge}(z) \cos \vartheta + YF^{\wedge}(z) \sin \vartheta + Z\varphi''(r, z) .$$

Comparing with Equation (1) we conclude that the coefficients a, b, c for the surface of the cylinder are given by

$$c\ (R, z) = \varphi''(R, z) \quad (4)$$

$$a\ (R, \vartheta, z) = F^{\wedge}(z) \cos \vartheta \quad (5)$$

$$b\ (R, \vartheta, z) = F^{\wedge}(z) \sin \vartheta . \quad (6)$$

The directions of the a, b, c axes are parallel to those of the X, Y, Z axes. The origin of the a, b, c space (image space) may be chosen at will. The reference potential, with which the potential of a point P is compared, is the mean value of the potential at $z = +\infty$ and $z = -\infty$.

It follows from Equations (5) and (6) that the image surface has the c-axis as the axis of rotational symmetry. In Fig. 4 we have drawn the intersection of the infinite cylinder with the x-z plane and, in the same figure, the intersection of its image surface with the a-c plane. The correspondence between a point P of the cylinder surface and the point P′ of the image surface is indicated by a straight line joining P and P′.

The parts of the cylinder that are a great distance from the dipole have their image approximately in two points of the image surface, namely, P_1 and P_2.

IV. THE POTENTIAL DISTRIBUTION ON A CLOSED (FINITE) CYLINDER

In Appendix IV we have given the method of calculation for the potential distribution on the surface of a cylinder bounded by two planes $z = -1.5$ R and $z = 2.2$ R. This can be done starting from the results of Appendices II and III using the method of electrical images. The results are represented in Figs. 5 and 6 for a dipole parallel to the axis, and in Figs. 7 and 8 for a dipole perpendicular to the axis of the cylinder. Notations are analogous to those for the infinite cylinder, but the index b denotes that we have a closed cylinder. We have, for example:

$$\varphi_b^{\wedge}(r, \vartheta, z) = F_b^{\wedge} \cos \vartheta . \quad (7)$$

It should be noted that the planes $z = -1.5$ R and $z = 2.2$ R are now part of the surface of the body while they are situated in the interior of the body for

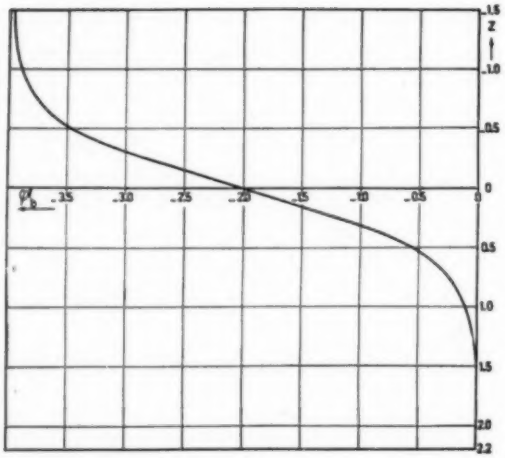

Fig. 5.

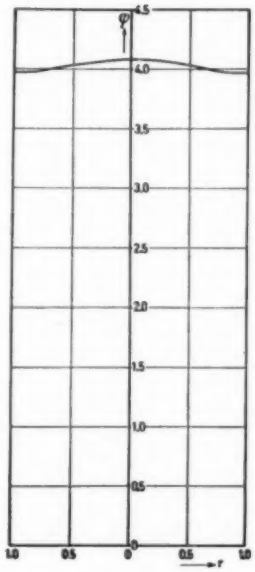

Fig. 6.

Fig. 5.—The potential $\varphi_b^{''}(R, z)$, caused by a dipole parallel to the axis of the finite cylinder on its surface, as a function of z.

Fig. 6.—The potential, caused by a dipole parallel to the axis of the finite cylinder on the boundary plane z = −1.5 R, as a function of r.

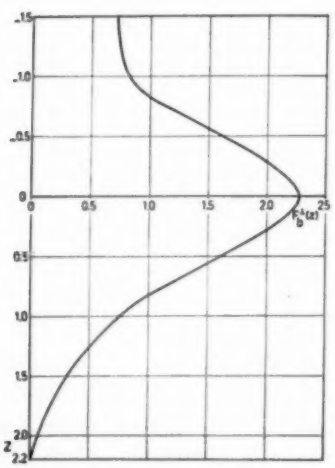

Fig. 7.

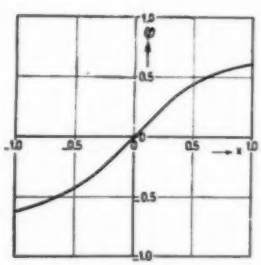

Fig. 8.

Fig. 7.—The potential $F_b^{\wedge}(z)$, caused by a dipole in the x-direction on the generating line x = 0, y = 1 of the surface of the finite cylinder, as a function of z.

Fig. 8.—The potential, caused by a dipole in the x-direction on the boundary plane z = −1.5 R, as a function of x (on the line y = 0, z = −1.5 R).

the infinite cylinder. We see from the figures that the differences with the infinite cylinder are not very great. (Compare Fig. 5 with Fig. 2 and Fig. 7 with Fig. 3.)

In Fig. 9 and Fig. 10, we have given diagrams of the equipotential lines on the surface of the cylinder for the parallel and the perpendicular dipoles, respectively.

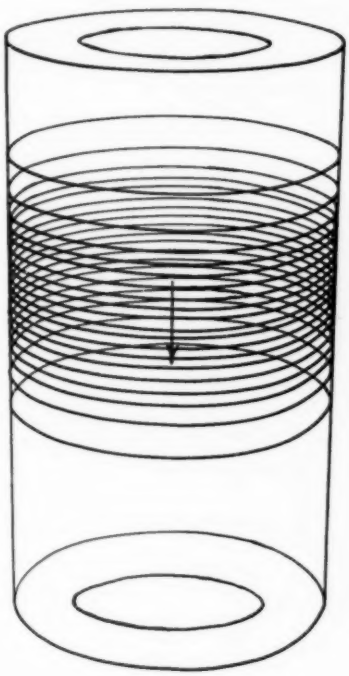

Fig. 9.

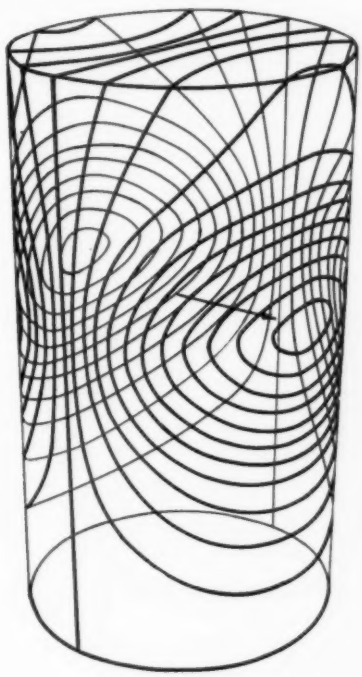

Fig. 10.

Fig. 9.—Equipotential lines on the cylinder surface for a dipole parallel to the axis. Two succeeding equipotential lines have a potential difference of 0.2.

Fig. 10.—Equipotential lines on the cylinder surface for a dipole perpendicular to the axis. Two succeeding equipotential lines have a potential difference of 0.2.

We can again represent the potential distributions by means of an image surface. The center of the lower boundary plane ($z = 2.2$ R) will be taken as reference point Q, where the potential of the finite cylinder is taken to be zero. As in Section III, the values of a, b, and c for the surface of the cylinder follow from the potential distributions caused by dipoles in the x, y and z directions. Likewise, the image surface has rotational symmetry about the c-axis. In Fig. 11, we have drawn the intersection of the cylinder with the x-z plane and in the same figure, the intersection of its image surface with the a-c plane. The correspondence between points of body and image surface is indicated in the same way as in Fig. 4.

The image surface does not differ very much from a sphere. It is remarkable that no visible edges of the image surface correspond to the edges of the cylinder. The lower end of the cylinder (especially the lower boundary plane) has its image nearly in one point—the lowest point of the image surface. This means that this part of the cylinder shows hardly any potential differences.

V. THE POTENTIAL DISTRIBUTION ON TWO PARALLEL PLANES

The field of a dipole (at the origin of a Cartesian coordinate system) between two parallel planes $y = A$ and $y = -3$ A can be calculated with the method of electrical images discussed in Appendix IV. We have represented the results by means of an image surface in the same way as in Sections III and IV (Fig. 12). The two parallel planes can be considered as a model of an extremely flattened trunk. The heart is placed at one-fourth of the distance between the front plane and the back plane. It is seen that this results in a large asymmetry of the image surface. The image surface has the b-axis as the axis of rotational symmetry.

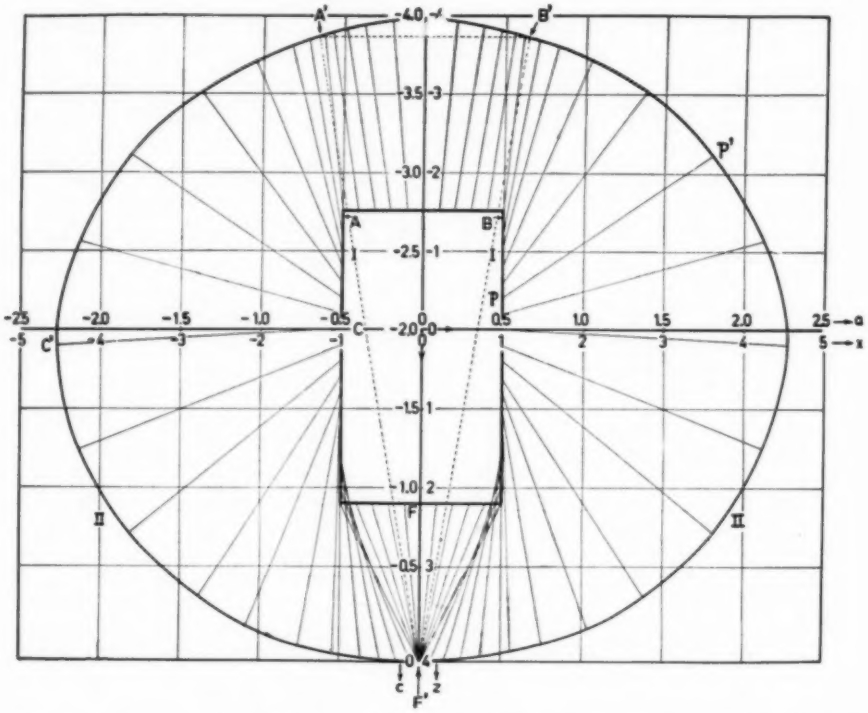

Fig. 11.—The image surface of the finite cylinder shown in Fig. 1. *I*, Intersection of the cylinder with the x-z plane. *II*, Intersection of the image with the a-c plane. The correspondence between a point *P* of the cylinder and *P'* of the image surface is indicated by a straight line.

VI. EXAMPLES OF THE USE OF THE IMAGE SURFACE

With the aid of the image surface, several problems can be numerically solved. Its use is analogous to that of the Einthoven triangle. The potential difference between two points of the body surface is equal to the projection of the heart vector on the line joining their *images* (not the points themselves) *multiplied by the length of this image-line.* In the following paragraphs, a few examples are given for the finite, closed cylinder (Fig. 11).

A.—It is easy to draw in Fig. 11 the triangle analogous to that of Einthoven. The arms correspond to the points A and B in the symmetry plane, about 0.1 R below the upper boundary plane of the cylinder, the (left) foot corresponds to the center F of the lower boundary plane. It appears that the triangle A'B'F' is not equilateral but very narrow. As a consequence of this,

the potential difference between A and B (Lead I) is relatively small, for it is equal to the product of the projection of the heart vector on A′B′ and the length of A′B′. This length is much smaller than A′F′ = B′F′. Conversely, if the leads are given it is concluded from the narrow triangle that the horizontal component of the heart vector is large.

The analogue of the equilateral tetrahedron can also be constructed, accepting that the back electrode is situated just behind the dipole (heart). Although in Fig. 11 only a plane drawing is given, the rotational symmetry of the cylinder permits the position of the image of the back electrode to be found. To this end, the points C and C′ have to be rotated 90 degrees about the symmetry axis till they lie behind the dipole. C′ must then be combined with the apices of the triangle A′B′F′, mentioned previously.

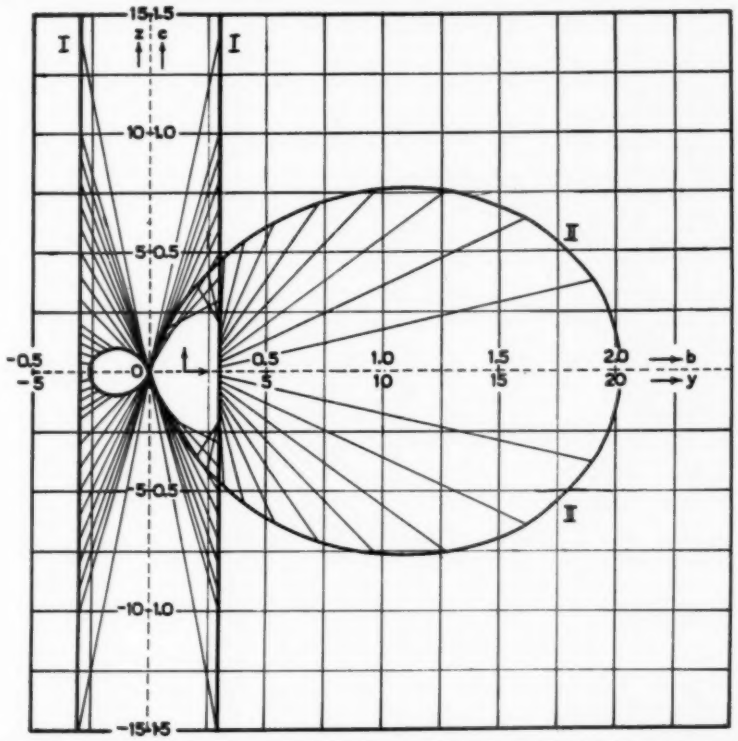

Fig. 12.—The image surface of two parallel planes with an eccentric dipole. *I*, Intersection of the two planes with the y-z plane. *II*, Intersection of the image surface with the b-c plane. The planes are placed at $y = \pm 3$; the dipole at $y = 1.5$, $z = 0$.

B.—If the heart vector is perpendicular to the axis of the cylindrical trunk, its projection on a vertical generating line is zero. The conclusion that the potential difference between the ends A and B of such a line (Fig. 13) be zero should be incorrect. The projection of the heart vector has to take place on the line A′B′ in the image space, and it appears that the potential difference between A and B is 50 per cent of that between the diametral points A and a of the top surface.

C.—We can calculate the potential difference between two diametral points p and P (Fig. 13) of the cylinder at the same height as a function of their height, the heart vector being horizontal. This potential difference is not independent of this height, as is the projection of the heart vector (dipole) on the line joining the diametral points. Its variation ranges from 27 per cent for aA to 0 per cent for bB of its maximum value, which is attained nearly at the same height as the heart. This potential difference is not inversely proportional to the square of the distance of the electrodes to the heart, nor to the square of the distance of the line joining them to the heart. This may be easily verified by the reader.

D.—If it is assumed that the projection of the heart vector on a line joining two electrodes is a measure of the potential difference between these electrodes, an error is made that depends on various circumstances. The following numerical example gives an idea of the error that can be made.

A heart vector making an angle of 45 degrees with the symmetry axis of the cylinder (pointing downward) gives potential differences between the "arms" (see *A*) and between an arm and the feet of 130 and 330 in an arbitrary measure. This can be deduced from Fig. 11. If we do not remember that these values have to be deduced, using the image surface in the correct manner, we may be inclined to suppose that the ratio of the aforementioned values 130/330 is the ratio of the projection of the heart vector on a horizontal and a vertical line, respectively. In this way the angle of the vector with the vertical line is computed to be 21 degrees instead of 45 degrees.

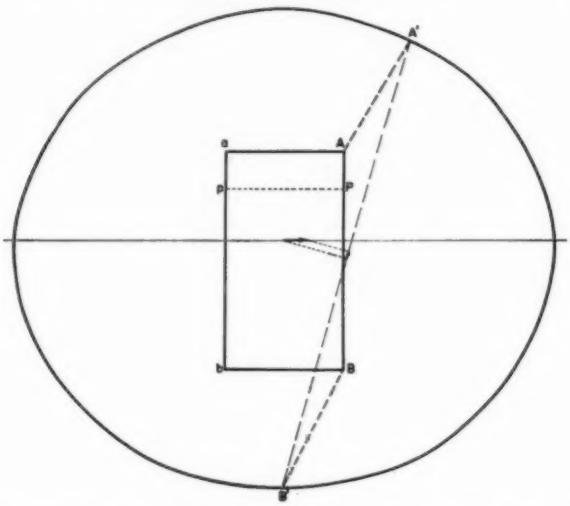

Fig. 13.—Illustration of the use of the image surface for a finite (closed) cylinder.

VII. DISCUSSION

Our models differ from the human body in many respects. Their shape and the position of the heart are not in accordance with the facts and a serious disadvantage is that the electrical heterogeneity of the human body is not taken into account. A much better approximation is the model we used previously.[3] The models referred to in the present paper, however, have an advantage in that the calculations give the image surface in a simple mathematical form, in such a way that it can be evaluated numerically.

The Einthoven triangle and its spatial generalization, the regular tetrahedron,[7] are based on the assumption of a homogeneous body, either extending infinitely or spherical. They are just as correct models as any other, though very imperfect ones. If a geometric shape has to be chosen, the closed cylinder is a much better approximation to the body shape than the sphere.

Our mathematical considerations allow us to draw some general conclusions as to the relation of the shape of the image surface to the shape of the body surface. A protruding part of the body surface, such as an arm or a leg, nearly corresponds to a single point in the image space. This is shown in the case of the infinite cylinder, the infinitely long ends of which are represented as one point (P_1 and P_2) of the image surface (Fig. 4). In the case of the extremity

leads it is therefore arbitrary *where* the electrode is placed on arm or leg. All points of the arm (or leg) are in the image space identical, as if shriveled up to one point.

An inward displacement of the body surface causes an outward displacement of the image surface at the same side. This is seen when the open and the closed cylinders are compared. Analogous to an inward displacement of the body surface is a displacement of the heart towards it. The outward displacement of the image surface caused by it is shown by Fig. 12 for the parallel planes, where this surface has a protruding part at the side nearest the heart. This gives an idea of the deformation of the image surface to be expected if the heart were situated eccentrically in a cylinder. The same must be true in the human body where the heart is situated near the frontal thoracic wall. The image surface of the human body has a protruding part at the frontal side. Consequently, there is a large potential difference between a precordial electrode and an indifferent electrode anywhere on the body surface according to the rules given in the preceding pages. The nearer the "heart," that is the dipole, is situated to the body surface the more protrudes the corresponding part of the image surface. The shape of the latter will, therefore, depend for the greater part on the position of the dipole. This position may vary considerably inside the heart and as its dimensions cannot be neglected, the image surface differs appreciably for different parts of the heart. This is especially true for the protruding part and therefore for precordial electrodes. It is to be expected that for these cases the description of the phenomena with a single image surface will not be a sufficient approximation.

It should be possible to calculate the image surface in a simple case, the heart lying near the body surface by proceeding from the case of the parallel planes. With two other pairs of planes the space might be bounded such that a rectangular prism is formed in which the heart is situated close to one of the planes. This requires, however, rather extensive calculations, which we have not carried out.

SUMMARY

A mathematical treatment of the dipole field in a bounded space is given for a few simple cases. The potential at the surface is calculated for an open and for a closed cylinder with the dipole on its axis, and for an infinite layer bounded by two parallel planes, the dipole being situated nearer to one plane than to the other. The medium is assumed to be homogeneous. The image surface introduced in a previous paper is calculated and represented in Figs. 4, 11, 12, and 13. A few examples illustrate the use of this surface.

APPENDIX I. MATHEMATICAL FORMULATION OF THE PROBLEM: METHOD OF SOLUTION

We now give the method used to calculate the potential φ in an infinite cylinder, discussed in Section II. φ must satisfy the potential equation which we write in cylindrical coordinates

$$\frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial \varphi}{\partial r}\right)+\frac{1}{r^2}\frac{\partial^2 \varphi}{\partial r^2}+\frac{\partial^2 \varphi}{\partial z^2}=0\,. \tag{A 1}$$

The boundary condition for a cylinder of radius R reads

$$\left(\frac{\partial \varphi}{\partial r}\right)_{r=R} = 0 \quad . \tag{A 2}$$

In the neighborhood of the origin φ must obey the expression

$$\varphi = \vec{p} \cdot \vec{\rho}/\rho^3 = p \cos \gamma/\rho^2, \vec{\rho} \simeq 0 \tag{A 3}$$

($\vec{\rho}$ is the radius vector from the origin; $\rho = \sqrt{r^2 + z^2}$.) Using the standard method of separation of the variables r, ϑ, z, in (A 1), we obtain a potential which satisfies (A 1) everywhere. This potential can be expressed in the following form (Fourier series and Fourier integral)

$$\varphi\,(r, \vartheta, z) = \sum_{n=-\infty}^{\infty} \exp\,(in\vartheta) \int_{-\infty}^{\infty} A_{n,\alpha}\, I_n\,(\alpha r) \exp\,(i\alpha z)\, d\alpha \tag{A 4}$$

$A_{n,\alpha}$ depends only on n and α. $I_n\,(\alpha r)$ is a Bessel function of order n (see notation of Ref. 6, p. 25 ff.). We desire a solution (A 4) which satisfies the boundary condition

$$\left(\frac{\partial \varphi}{\partial r}\right)_{r=R} = g\,(\vartheta, z) \quad . \tag{A 5}$$

Assuming $g\,(\vartheta, z)$ can be expanded in a Fourier series

$$g\,(\vartheta, z) = \sum_{n=-\infty}^{\infty} \int_{-\infty}^{\infty} B_{n,\alpha} \exp\,(in\vartheta) \exp\,(i\alpha z)\, d\alpha \tag{A 6}$$

then, from (A 4), (A 5) and (A 6), the value of $A_{n,\alpha}$ follows

$$A_{n,\alpha} = B_{n,\alpha}/\alpha\, I_n^1\,(\alpha) \quad . \tag{A 7}$$

This value of $A_{n,\alpha}$ substituted in (A 4) gives a potential $\varphi\,(r, \vartheta, z)$ which satisfies the potential equation (A 1) everywhere within the cylinder and which satisfies the boundary condition (A 5). However, we want to calculate a potential φ which satisfies (A 1) everywhere within the cylinder except in the origin, where it must have the singularity (A 3).

Furthermore, the boundary condition (A 2) must be satisfied. This problem can be reduced to the preceding one by putting

$$\varphi = \varphi_0 + \varphi_1 \tag{A 8}$$

where

$$\varphi_0 = \vec{p} \cdot \vec{\rho}/\rho^3 \quad \text{(in entire space).} \tag{A 9}$$

φ is a solution of (A 1) with the singularity (A 3) and the boundary condition (A 2). It follows that φ_1 is a solution of (A 1) without the singularity and with the boundary condition (A 5), where

$$g\,(\vartheta, z) = -\left[\frac{\partial}{\partial r}\left(\vec{p} \cdot \vec{\rho}/\rho^3\right)\right]_{r=R} \quad . \tag{A 10}$$

Hence our problem has been reduced to finding the Fourier expansion (A 6) of this expression and calculating (A 4) with the coefficients obtained.

APPENDIX II. POTENTIAL DISTRIBUTION OF A DIPOLE PARALLEL TO THE AXIS OF AN INFINITE CYLINDER

The problem of Appendix I is specialized to the extent that the vector $\vec{p}$ of (A 9) is now a vector in the direction of the z-axis, and φ_0 can be expressed as

$$\varphi_0 = pz\,(r^2 + z^2)^{-\frac{3}{2}}. \tag{A 11}$$

According to (A 10) the function $g(\vartheta, z)$ becomes

$$g(\vartheta, z) = 3\,pRz\,(R^2 + z^2)^{-\frac{5}{2}}. \tag{A 12}$$

To obtain the Fourier expansion of $g(\vartheta, z)$ we use the formula given in Ref. 6, p. 163

$$\frac{1}{2}\,\frac{1}{(z^2 + R^2)^{\nu + \frac{1}{2}}} = \frac{1}{2\pi}\int_{-\infty}^{\infty} \exp(-i\alpha z)\left(\frac{|\alpha|}{2R}\right)^{\nu}\frac{\Gamma(\frac{1}{2})}{\Gamma(\nu + \frac{1}{2})}\,K_{\nu}(R|\alpha|)\,d\alpha, \tag{A 13}$$

where $\quad \operatorname{Re}\nu > -\frac{1}{2}$.

From (A 13) we obtain, by partial integration and the use of some appropriate formulas for the K_ν functions (see Ref. 6, p. 29)

$$3pRz\,(R^2 + z^2)^{-\frac{5}{2}} = \frac{ipR}{\pi}\int_{-\infty}^{\infty}\exp(i\alpha z)\,\frac{d}{d\alpha}\left[K_2(R|\alpha|)\alpha^2/R^2\right]d\alpha$$

$$= -\frac{ip}{\pi}\int_{-\infty}^{\infty}\exp(i\alpha z)\alpha|\alpha|K_1(R|\alpha|)\,d\alpha. \tag{A 14}$$

The coefficients $B_{n,\alpha}$ according to (A 6) that are derived from (A 14), are

$$B_{n,\alpha} = \begin{cases} -(ip/\pi)\alpha|\alpha|K_1(R|\alpha|), & \text{if } n = 0 \\ 0, & \text{if } n \neq 0. \end{cases} \tag{A 15}$$

Hence we see that the Fourier series has only a single term. From the values for $B_{n,\alpha}$ we get, according to (A 15) and (A 7), using the formula

$$I_0^1(\alpha R) = I_1(\alpha R) \qquad \text{(see Ref. 6, p. 29)},$$

$$A_{n,\alpha} = \begin{cases} -(ip|\alpha|/\pi)K_1(R|\alpha|)/I_1(R\alpha), & \text{if } n = 0 \\ 0, & \text{if } n \neq 0. \end{cases} \tag{A 16}$$

For φ_1 we obtain, after a simple transformation from (A 4)

$$\varphi_1(r, z) = (2p/\pi)\int_0^{\infty}\alpha K_1(\alpha R)[I_0(\alpha r)/I_1(\alpha R)]\sin\alpha z\,d\alpha. \tag{A 17}$$

The complete solution of our problem is given by (A 8). The value of $\varphi_1(r, z)$ was calculated numerically for a series of values of z for $r = R$ and for a series of values of r for $z = z_0 = -1.5\,R$. The results for $\varphi(R, z)$ are given in Fig. 2. (The error is less than 1 per cent.) In these results we have taken $p = 1$. We remark that

$$\lim_{z = \infty}\varphi_1(R, z) = 2; \quad \lim_{z = -\infty}\varphi_1(R, z) = -2 \tag{A 18}$$

This can be deduced rigorously from (A 17), but it can also be proved without any explicit calculation.

APPENDIX III. POTENTIAL DISTRIBUTION OF A DIPOLE PERPENDICULAR TO THE AXIS OF AN INFINITE CYLINDER

We take $\vec{p}$ in the direction of the x-axis. (A 9) then becomes

$$\varphi_0 = pr \cos \vartheta (r^2 + z^2)^{-\frac{3}{2}}. \tag{A 19}$$

The function g (ϑ, z) consequently has the form

$$g(\vartheta, z) = -p \cos \vartheta (R^2 + z^2)^{-\frac{5}{2}} (z^2 - 2R^2). \tag{A 20}$$

By partial integration and the use of appropriate formulas for the K_ν- functions,[6] we find the Fourier expansion of g (ϑ, z) from (A 13) and (A 14), which we give by the coefficients $B_{n,\alpha}$:

$$B_{n,\alpha} = \begin{cases} (p/2\pi)[\alpha^2 K_0(R|\alpha|) + |\alpha| K_1(R|\alpha|)/R], & \text{if } n = \pm 1 \\ 0 & , \text{ if } |n| \neq 1. \end{cases} \tag{A 21}$$

After some reductions (see Ref. 6, the formulas on p. 29), $A_{n,\alpha}$ becomes, according to (A 7),

$$A_{n,\alpha} = \begin{cases} \dfrac{p}{2\pi} \dfrac{\alpha^2 K_0(R|\alpha|) + |\alpha| K_1(R|\alpha|)/R}{\alpha I_0(R\alpha) - I_1(R\alpha)/R}, & \text{if } n = \pm 1 \\ 0 & , \text{ if } |n| \neq 1. \end{cases} \tag{A 22}$$

We obtain from (A 4), after some reductions, the expression for φ_1:

$$\varphi_1(r, \vartheta, z) = p \cos \vartheta \int_0^\infty \frac{2\alpha}{\pi} \frac{\alpha K_0(R\alpha) + K_1(R\alpha)/R}{\alpha I_0(R\alpha) - I_1(R\alpha)/R} I_1(\alpha r) \cos \alpha z \, d\alpha. \tag{A 23}$$

The integral in (A 23) was calculated for a number of values of z for r = R and for a number of values of r for $z = z_0 = -1.5$ R. The results for φ (r = R, ϑ = o, z) and φ (r, ϑ = o, $z = z_0$) are represented in Fig. 3. (The error is less than 1 per cent.)

APPENDIX IV. POTENTIALS OF DIPOLES IN A FINITE CYLINDER: METHOD OF ELECTRICAL IMAGES

If we have the solution of the potential problem for an infinite cylinder with a dipole $\vec{p}$ placed at the origin, we can derive the solution of the problem for a finite cylinder from it. Suppose the boundary planes are z = a and z = b (a < o < b) and that φ (r, ϑ, z) is the solution for the infinite cylinder. The solution for the finite cylinder is given by the sum (l = a + b)

$$\varphi_b(r, \vartheta, z) = \sum_{n=-\infty}^{\infty} \Big[\varphi(r, \vartheta, z - 2nl) + \varphi(r, \vartheta, 2a - z - 2nl) \Big]. \tag{A 24}$$

This series gives the sum of an infinite series of electrical images. We assume that the potential in any term is zero at a certain point of the body, for example, the center of the lower boundary plane. It can then be shown that no convergence difficulties exist. The potential (A 24) represents the potential of a series of dipoles as shown in Fig. 14. Hence, it satisfies the potentail equation in the interior of the finite cylinder and has the prescribed dipole singularity at the origin. As each of the terms in (A 24) satisfies the boundary condition $\left(\frac{\partial \varphi}{\partial r}\right)_{r=R} = 0$, it is also satisfied for the sum φ (r, ϑ, z). The series of images has now been chosen in such a way that the boundary condition $\left(\frac{\partial \varphi}{\partial z}\right)_{z=z_0} = 0$ is also satisfied for the upper and lower boundary planes.

The dipole, with its images, is a distribution of current sources symmetrical with respect to both the $z = a$ and the $z = b$ planes, from which the boundary condition follows. For the actual calculation of the potential in the finite cylinder with the aforementioned dimensions, it is sufficient to consider only a few image dipoles. By an estimation of the behavior of the potential in the infinite cylinder, it can be proved that the other image dipoles make only a negligible contribution to the sum.

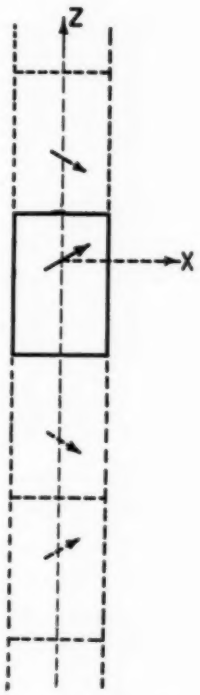

Fig. 14.—Illustration of the method of electrical images. The full lines indicate the intersection of the cylinder with a plane through the axis. The arrow indicates the dipole. The dotted lines indicate the electrical images, the dotted arrows the images of the heart vector.

The same method of electrical images has been used to calculate the field of a dipole between two parallel planes. In that case, we must calculate the sum of the fields in free space of a series of dipoles.

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THE EFFECT OF PHOSPHORYLATED HESPERIDIN* ON EXPERIMENTAL ATHEROSCLEROSIS

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THE mechanism by which the intimal deposition of cholesterol takes place in atherosclerosis is not clearly established. Although stress, the level of the serum cholesterol, and the form in which the circulating cholesterol is carried have been implicated, little attention has been paid to the role of hyaluronidase in altering the permeability of the intima to cholesterol. This experiment was designed to study the effect of the antihyaluronidase, phosphorylated hesperidin, on the aortic deposition of cholesterol in experimental atherosclerosis.

METHODS

To induce atherosclerosis, male albino rabbits, of approximately the same age and weight each, received 5 Gm. of cholesterol dissolved in ether and poured over an ad lib. quantity of Purina rabbit chow three times each week. In addition to cholesterol feeding, the six pairs of rabbits in Group 1 were given 40 mg./kg. of phosphorylated hesperidin intraperitoneally five times a week for four weeks. Group 2 animals (8 pairs) received in addition to cholesterol 50 mg./kg. of phosphorylated hesperidin intraperitoneally three times a week for four weeks. Group 3 rabbits were fed cholesterol for eight weeks and in addition received 100 mg. of phosphorylated hesperidin intraperitoneally three times each week for this period. Control Group 4 was fed cholesterol in similar fashion but received sterile saline intraperitoneally three times each week for four weeks (Group 4-A) and eight weeks (Group 4-B), respectively.

All animals were weighed weekly and total serum cholesterol levels were obtained each week. Prior to cholesterol feeding and at the time of sacrifice the hematocrit, urea nitrogen, total protein, phospholipid and cholesterol partition levels were obtained. At sacrifice all tissues were examined grossly and the entire aorta removed and preserved in formalin. After several weeks' fixation, the aortas were graded for atherosclerosis on a 1 to 4-plus basis by two independent observers who had no access to data about the experiment. These data are summarized in Table I.

From the Addison H. Gibson Laboratory of the University of Pittsburgh School of Medicine.

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TABLE I. THE EFFECT OF PHOSPHORYLATED HESPERIDIN ON EXPERIMENTAL ATHEROSCLEROSIS

	MEAN WT. GAIN DURING EXPERIMENT (GM.)	MEAN FINAL TOTAL CHOLESTEROL (MG. %)	MEAN FINAL FREE CHOLESTEROL (MG. %)	MEAN FINAL CHOLESTEROL ESTERS (MG. %)	MEAN FINAL LIPID PHOSPHORUS (MG. %)	MEAN AORTIC ATHEROSCLEROSIS
Group 1:	Cholesterol fed plus 40 mg./kg. phosphorylated hesperidin 5 times per week intraperitoneally for 4 weeks.					
(6 pairs)	120	710	200	510	37	1.0 +
Group 2:	Cholesterol fed plus 50 mg./kg. phosphorylated hesperidin 3 times per week intraperitoneally for 4 weeks.					
(8 pairs)	145	860	270	590	45	1.8 +
Group 3:	Cholesterol fed plus 100 mg. phosphorylated hesperidin 3 times per week intraperitoneally for 8 weeks.					
(6 pairs)	110	1240	410	830	84	1.2 +
Group 4-A:	Cholesterol fed plus intraperitoneal saline 3 times per week for 4 weeks.					
(4 pairs)	200	1100	255	845	62	1.0 +
Group 4-B:	Cholesterol fed plus intraperitoneal saline 3 times per week for 8 weeks.					
(4 pairs)	380	1210	390	820	58	3.8 +

DISCUSSION

Groups 1 and 2 receiving phosphorylated hesperidin had somewhat lower mean total cholesterol and cholesterol esters at the end of four weeks than did the intraperitoneal-saline-treated control Group 4-A. However, the mean weight gain was 200 grams in the control group and 120 grams in Group 1 and 145 grams in Group 2. This variation in weight gain could explain these variations in cholesterol level. It is significant to note that the saline-treated control group at four weeks had as little atherosclerosis as either Group 1 or 2 receiving phosphorylated hesperidin.

Group 3 receiving cholesterol and 100 mg. of phosphorylated hesperidin three times a week for eight weeks had cholesterol and lipid phosphorus levels similar to those of control Group 4-B. However, the control group had distinctly more aortic atherosclerosis than did the comparable hesperidin-treated group (3.8 + to 1.2 +). However, this decrease in aortic atherosclerosis cannot be directly attributed to the drug, as the control group evidenced a mean weight gain of 380 grams compared to 110 grams in the hesperidin-treated group. As was first shown by Firstbrook,[1] the development of atherosclerosis may be closely related to weight gain in this type of experiment.

SUMMARY

The intraperitoneal administration of phosphorylated hesperidin failed to influence the development of aortic atherosclerosis in rabbits fed cholesterol for four weeks. After eight weeks of feeding cholesterol and the administration of 100 mg. of phosphorylated hesperidin three times a week, distinctly less aortic atherosclerosis was evident. However, this may be due to the sharply decreased weight gain seen in the animals receiving phosphorylated hesperidin.

The author wishes to express his appreciation for the cooperation of Mrs. Grace L. Rhodes, Miss Gene Garrity, Mr. T. F. Hatch, Jr., and Dr. William F. Baird in this study.

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Clinical Reports

PROLONGED DEPRESSION OF ATRIOVENTRICULAR CONDUCTION CAUSED BY LARGE DOSAGES OF PROTOVERATRINE

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PROTOVERATRINE, a purified derivative of *Veratrum album*, has been found to be a valuable but potentially toxic hypotensive agent.[1] In human beings, the use of veratrum alkaloids has been hindered by their toxicity, but recently certain clinical trials have been undertaken. Protoveratrine has been found to be the best tolerated of the veratrum alkaloids in man because satisfactory reductions in blood pressure are possible without exceeding the emetic threshold. In an effort to reduce the untoward reactions of protoveratrine, Hoobler and associates[2] devised a program using an effective oral dosage reinforced by additional small dosages. With their method, satisfactory prolonged reductions in blood pressure were obtained with only rare emetic side effects.

During the course of clinical trials of protoveratrine,* an inadvertent overdosage of two and one-half times the prescribed amount was given to a patient being treated according to the regimen advocated by Hoobler and associates.[2] This afforded the opportunity to study the toxic manifestations of large doses administered orally as illustrated in the case herein reported.

CASE REPORT

A 51-year-old white businessman was admitted to University Hospital for the first time on Sept. 29, 1952, complaining of headaches and a blind spot in his right eye. He had been well until four years before admission when the onset of severe headaches led to the discovery of his hypertension. Four months prior to entry, he developed severe precordial pain of short duration, and an electrocardiogram at that time revealed left ventricular enlargement only. Two months later, evidence of minimal heart failure was found, and he was placed on digitalis, ammonium chloride, and a low-sodium diet. He improved on this regimen but continued to have headaches and for six weeks before admission had insomnia which persisted despite heavy sedation. Five days prior to admission, he developed a right visual scotoma due to vasospastic retinitis. He was referred to the hospital for evaluation of the persistent hypertension and the progressive eye-ground changes. Ambulant arterial pressure before admission ranged from 240/150 to 280/180 mm. Hg. He denied cough, peripheral edema, exertional dyspnea, palpitation, recurrence of chest pain, or urinary difficulties. There had been a 13-pound-weight loss in six months.

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Past history and system review were noncontributory. Family history revealed that his father expired at 63 from a stroke; his mother died at 53 with Bright's disease and hypertension, and one of eight siblings had hypertension.

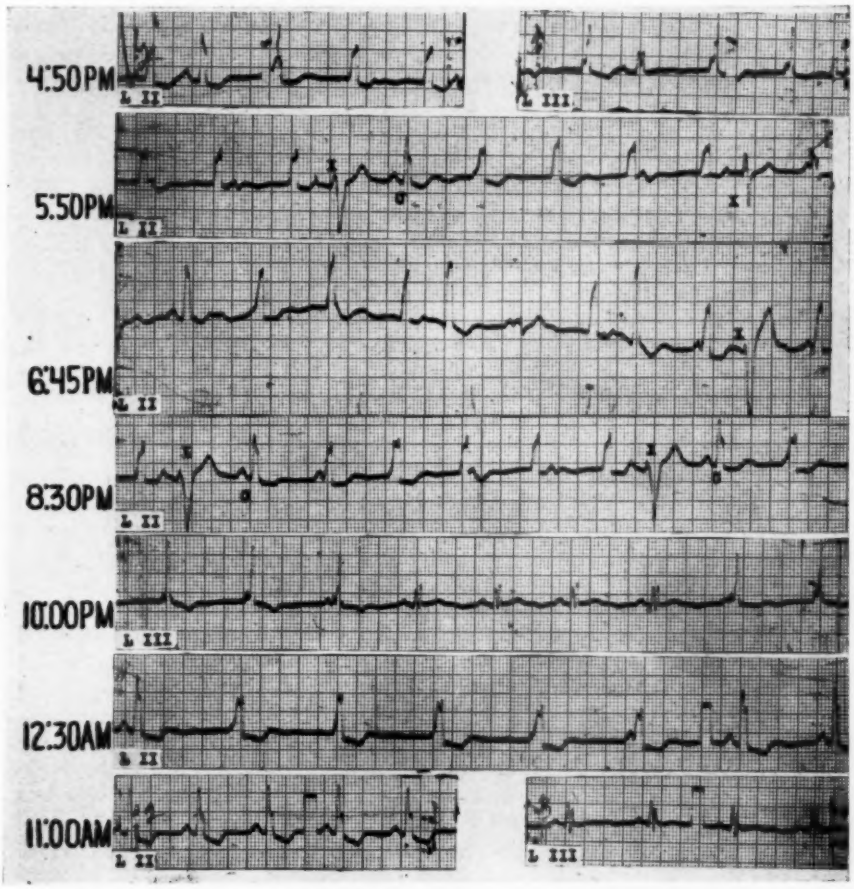

Fig. 1.—Serial electrocardiograms in protoveratrine intoxication demonstrating the change from complete atrioventricular dissociation to normal sinus rhythm. *X*, Premature ventricular beats, and *C*, conducted sinus beats with a normal ventricular response.

Physical examination revealed a well-developed, well-nourished white man in no apparent distress. Temperature was 100° F.; weight, 134½ pounds; respirations, 20; pulse, 120; and arterial pressure, 258/166 mm. Hg. Funduscopic examination revealed marked tortuosity and arteriovenous nicking with numerous small hemorrhages bilaterally. There was slight blurring of the right disc margin, marked arteriolar spasm bilaterally, and a small ischemic area in the region of the right macula. A well-delinated right-eye central scotoma was present on gross confrontation. Many fine inspiratory râles were heard at the right lung base. The heart was enlarged to the left with the point of maximal impulse in the left anterior axillary line; the rhythm was regular; A_2 greater than P_2 and M_2 greater than M_1; and there was a systolic gallop and a Grade 1 high-pitched blowing systolic murmur heard at the apex. The liver was palpable 2 cm. below the right costal margin. There was no lymphadenopathy. Extremities and neurologic examination were normal.

Laboratory data revealed hemoglobin, 13.3 Gm.; hematocrit, 42 per cent; white blood count, 9,900; 82 per cent neutrophils; 18 per cent lymphocytes. Smear normal. Urianalyses revealed S.G. 1.010 to 1.015; albumin 4-plus initially and 1 plus on two subsequent occasions; sugar 0;

microscopic occasional white bloodcells, 2 to 4 granular casts, and an occasional red blood cell. Nonprotein nitrogen was 45 mg. per cent. Phenosulfonphthalein test revealed 5 per cent excretion in 15 minutes and 35 per cent excretion in two hours. Electrocardiogram showed sinus tachycardia with normal atrioventricular and intraventricular conduction. There was evidence of left ventricular enlargement with some evidence of auricular enlargement. These represented little change from previous tracings three months earlier. Chest roentgenogram revealed left ventricular enlargement plus minimal pulmonary edema. An intravenous pyelogram was normal.

Hospital course: Blood pressure after admission ranged from 210/140 to 250/170 mm. Hg. A benzodioxane test was negative. The administration of 1 c.c. of Thiomerin resulted in a one-pound-weight loss without significant change in blood pressure. On the fifth hospital day, the patient was started on protoveratrine 0.75 mg. initially at 8 A.M. plus 0.25 mg. at 10 A.M. and 1 P.M. The initial dose was increased 0.25 mg. daily until the patient was receiving a total of 2.0 mg. Because of the onset of nausea, the dose was reduced to 1.75 mg. daily on the tenth hospital day. On the latter dosage, the blood pressure fell, ranging from 160/90 to 200/110 mm. Hg, with the disappearance of all symptoms except the scotoma which improved slowly.

After having stabilized the dose at 1.75 mg. daily without toxic signs, the patient was slowly digitalized with digitoxin. On the nineteenth hospital day, the patient inadvertently received 500 mg. protoveratrine tablets in place of 200 mg. tablets previously used, resulting in an initial dose of 3.125 mg. with a reinforcement dose of 0.625 mg. at 10 A.M. At noon, he complained of severe nausea and dizziness and his arterial pressure was 120/78 mm. Hg, pulse 74. A few minutes later, severe vomiting occurred and he was given 0.4 mg. of atropine subcutaneously and 1.2 mg. intravenously. This had no effect on his pulse of 66 which was regular and bounding; no immediate effect on blood pressure was noted; and the patient continued to retch despite diminished bowel activity as noticed by auscultation. The nausea continued for four hours. At 3 P.M., the blood pressure fell to 86/60, but rose within a few minutes to 102/72, above which level it remained. No mydriasis or dry mouth resulted from the atropine which was given. An electrocardiogram (Fig. 1) done at 4:30 P.M. revealed marked depression of atrioventricular conduction with complete atrioventricular dissociation. Although the sinus was still discharging impulses, the pacemaker was in the atrioventricular node or the bundle of His. At this time, there were many ectopic beats both auricular (blocked) and ventricular. At times, regularly, the sinus impulse occurred in the supernormal phase and a normally conducted beat occurred. Subsequent serial electrocardiograms (Fig. 1) showed the same mechanism of interference dissociation with diminishing numbers of ectopic beats. After the pacemaker shifted repeatedly from sinus node to atrioventricular node, in and out of complete dissociation, the sinus impulse finally became the pacemaker and the next morning the curves had resumed their former appearance.

Protoveratrine, 1.75 mg. daily, and digitoxin were resumed after one day's omission with as satisfactory a response as had been noted previously. The patient had no permanent effects from the overdosage and was discharged four days later on the above protoveratrine regimen. One month after discharge, he had a blood pressure ranging from 210/110 to 230/130 mm. Hg in mid-afternoon, was asymptomatic, and had resumed working. His ophthalmologist reported that the scotoma remained unchanged although it was less annoying. The hypertensive retinopathy was unchanged except for a new hemorrhage in the periphery of the right fundus.

DISCUSSION

Krayer and associates[1] found the toxic effects of protoveratrine in the hypodynamic mouse heart included one-half rhythm and atrioventricular dissociation. They also demonstrated that the hypotensive effect of protoveratrine was obtained secondary to bradycardia and vasodilatation; the bradycardia being due to efferent vagal influences with afferent stimuli originating centrally and in the thoracic viscera. Their toxicity studies in the completely denervated preparation revealed auricular standstill, ventricular bradycardia, and fibrillation.

Meilman and Krayer[3] using protoveratrine parenterally with doses of 2 to 3 μg/kg. noted the following transient cardiac arrhythmias in man: first degree

heart block, nodal rhythm, ventricular extrasystoles, bigeminy and Wenckebach phenomena. The arrhythmias were usually intermittent and periods of regular rhythm alternated with periods of prolonged P-R intervals or nodal beats. When the dose of protoveratrine which produced arrhythmias was given simultaneously with atropine, no arrhythmias appeared; yet, an arterial pressure fall occurred, although of a smaller degree. They also demonstrated the ability of intravenous atropine to rapidly reverse an established 2:1 heart block induced by protoveratrine. Hoobler and associates[4] and Meilman[5] have reported the reversibility of protoveratrine-induced bradycardia with atropine.

Since this patient was digitalized greater cardiac toxicity from the protoveratrine might be expected since the alkaloids can have an additive effect on impulse conduction and generation. Meilman and Krayer[3] showed that fully digitalized patients were more susceptible to cardiac arrhythmias at lower dosages of protoveratrine than were other patients. Hoobler and associates,[2] however, failed to notice any increased toxic effects from the administration of both drugs to the hypertensive person. It is noted that the major cardiac manifestation of toxicity in this patient was a profound, prolonged depression of atrioventricular conduction which was resistant to atropine. If excess vagal tone due to a combination of digitoxin and protoveratrine is postulated as the cause of the atrioventricular block, atropine should have abolished the block. Its failure to do so leaves two possible explanations: (1) the dosage of atropine was inadequate or (2) in addition to its vagotonic action, protoveratrine may have a local select depressant effect on atrioventricular conduction.

This patient improved remarkably on this drug after a five-day trial without medication during which his symptoms had remained unchanged. Simultaneously with the advent of effective treatment, evidence of pulmonary congestion disappeared (before redigitalization), chest discomfort and headache disappeared, and his sense of well-being improved remarkably. All cardiac and other manifestations of toxicity from the protoveratrine overdosage disappeared within 24 hours without any apparent ill effects, and the drug was resumed without incident.

SUMMARY AND CONCLUSIONS

1. The management of a case of severe hypertension of undetermined etiology using orally administered protoveratrine is described.

2. The toxic manifestations of an overdosage of protoveratrine and a brief discussion of the cardiac mechanisms involved are presented.

3. Massive dosages of protoveratrine may cause prolonged depression of atrioventricular conduction which is not abolished by atropine.

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CORONARY ANEURYSM WITH ARTERIOVENOUS FISTULA

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CASE REPORT

An 85-year-old veteran of World War I was first admitted to Shaughnessy Hospital in June, 1951, complaining of shortness of breath and swelling of the ankles. He had enjoyed good health until eighteen months prior to admission, at which time he had noticed dyspnea on exertion and mild dependent edema. He was treated by his local physician and put on digitalis.

Past history included malaria. There was no history of rheumatic fever or syphilis and no history of previous cardiovascular disease.

On admission he was dyspneic at rest, the liver was enlarged four finger breadths below the right costal margin, and edema was present one-third of the way up the tibia. There was no venous distension of the neck veins, cyanosis, or clubbing of the fingers. His cardiovascular system showed an irregular pulse of 80 and blood pressure 170/80 mm. Hg. The maximum cardiac impulse was in the sixth intercostal space, just outside the mid-clavicular line; there was a harsh Grade 4 systolic murmur heard over the whole precordium; no thrill was recorded. There were scattered râles in both lung bases. His peripheral arteries showed marked sclerosis. The electrocardiogram revealed auricular fibrillation and a left bundle branch block. X-ray and fluoroscopy of the chest showed marked cardiac enlargement, mainly left ventricular, with a cardiothoracic ratio of 18 over 29 cm. Calcification of the aortic valve was reported. His blood was Kahn negative.

A diagnosis of arteriosclerotic heart disease with auricular fibrillation and congestive failure was made. He responded well to therapy and was soon discharged.

In October 1951, he was readmitted with congestive failure, and the internist reported Grade 3 aortic systolic, Grade 2 aortic diastolic, and Grade 4 mitral systolic murmurs; no thrill was palpated. He again responded well to therapy and was discharged.

His last admission was in May, 1952, and he died within one-half hour of acute pulmonary edema.

At *necropsy* there was marked pulmonary edema; other significant findings were confined to the heart.

The heart weighed 554 grams and the enlargement was mainly due to left ventricular hypertrophy, but there was moderate hypertrophy and dilatation of the right ventricle and auricle. The right auricle appeared to show considerable hypertrophy. The tricuspid and pulmonary valves were normal. The leaflets of the mitral valve were slightly thickened, but not sclerosed, and the cusp margins not fused. The aortic valve cusps showed only slight calcification, spreading in one for 2 mm. into the cusp from its attachment. A second cusp showed calcareous nodules, while the third cusp was practically free. There was only slight coalescence of the commissures and no rolling of the free borders. There was no appreciable stenosis and no indication that this valve was incompetent. The lower part of the ascending aorta showed calcareous atherosclerotic plaques; the higher part was remarkably normal for so old a man. There was no suggestion of syphilis.

The ostium of the left coronary artery was normal in position and size. Apart from marked atherosclerosis and calcification of the main stem and the upper parts of the anterior descending branch, the left coronary artery was normal in size and distribution.

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The ostium of the right coronary artery was slightly larger than normal and funnel-shaped. Immediately beyond the aortic wall it became dilated (Fig. 1) by a fusiform enlargement to a diameter of 2 cm. This marked dilatation extended for approximately 5 cm. along the main

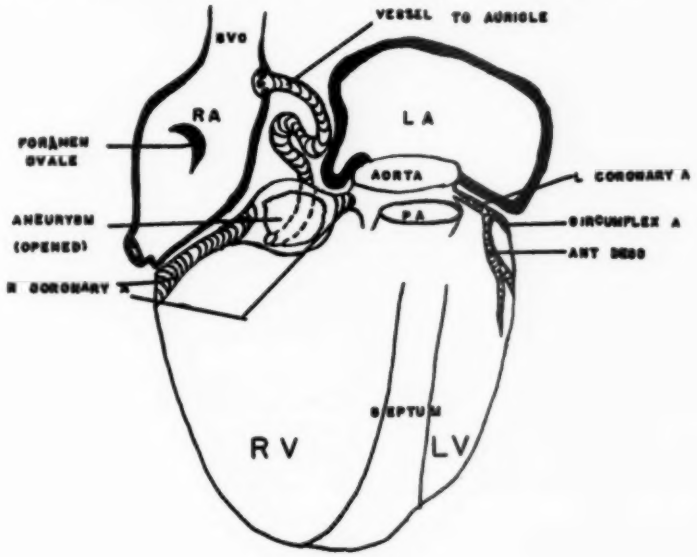

Fig. 1.

branch. It then showed a fairly abrupt relative narrowing to a diameter of 8 mm. Immediately before this point of relative narrowing, a large vessel opened by a small orifice from the postero-inferior aspect. This vessel was approximately 1.4 cm. in diameter and passed behind the aneurysm

Fig. 2.—Opening of aberrant vessel in right atrium.

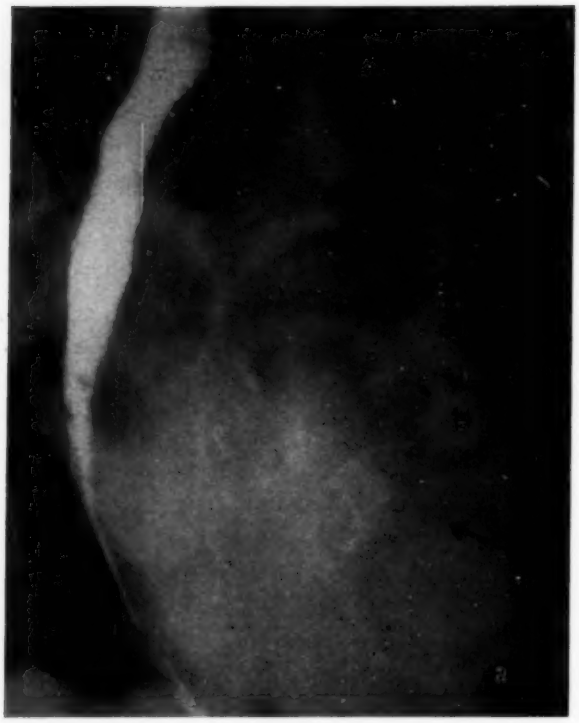

Fig. 3.—X-ray showing aneurysm.

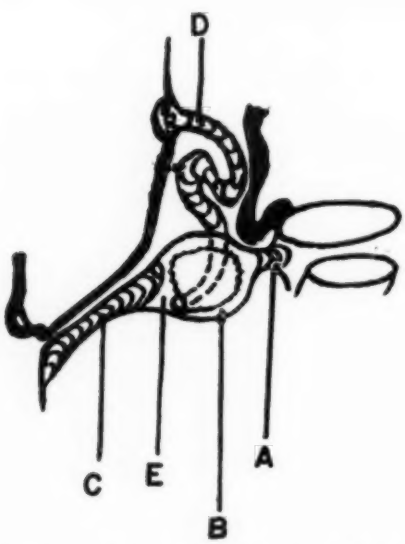

Fig. 4.—Diagram of the coronary artery showing position of the microscopic sections.

and followed a serpentine course, first between the aorta and the right auricle and later between the two auricles. It gave off no branches, but passed through the wall of the right auricle to terminate as a roughly hemispherical projection on the endocardium of the right auricle at the junction of the auricle with the superior vena cava (Fig. 2). This projection was calcareous and showed four small openings which connected with the bulbous termination of the vessel. When saline was injected with very little pressure into the vessel, jets of fluid spurted from the four orifices. This anomalous vessel was for the most part atherosclerotic and calcified with a few portions which were relatively thin and soft.

The x-ray pictures taken during life were re-examined in the light of these findings and it was seen that the shadow previously interpreted as a calcified aortic valve was in fact the calcified coronary aneurysm (Fig. 3).

The coronary sinus was explored and found to be in its normal position and traced into the right auricle near the junction of the inferior vena cava.

Thus the specimen showed (1) an aneurysmal dilatation of the right coronary artery with (2) an anomalous branch ending in the right auricle and constituting functionally an arteriovenous shunt. The anomalous vessel might be either an aneurysmally dilated aberrant coronary artery or a dilated vein resulting from rupture of a coronary aneurysm into a vein.

Sections were taken at *A*, *B*, *C*, *D*, and *E* (Fig. 4) and stained with hematoxylin and eosin and Verhoeff elastic tissue stain. At *A* there is a small amount of atherosclerosis, a well-defined internal and external elastic membrane, a few elastic fibers, and a considerable increase in connective tissue in the media. At *B* are marked calcification and degeneration; the media is thinned with only sparse fibers of elastic tissue and about the same amount of collagen as in *A*. The external elastic membrane is present but the internal membrane is destroyed in the degenerative process. The section at *C* is similar to *A*. *D* is similar to *B*, except that the wall is thinner but has a greater proportion of muscle. *E* is similar to *D* but the wall is even thinner. Thus, although the histology is obscured by atherosclerosis, the appearances of the anomalous vessel suggest that it is an artery and not a vein. Furthermore, it showed no connection with other coronary veins or sinuses.

Histology of the cardiac muscle revealed a few scattered patches of interstitial fibrosis but was otherwise normal.

The kidneys were normal in size, the surface very finely granular with a normal thickness of cortex. On microscopy, slight hyaline degeneration and medial sclerosis of arterioles were found, but nothing else of significance.

DISCUSSION

Aneurysms of the Coronary Arteries.—Aneurysm of the coronary arteries was first described by Bougon in 1812. An extensive search of the literature was made by Packard and Wechsler[1] in 1929, after observing a case of aneurysm of the left coronary artery with rupture. They found a total of twenty-eight reported cases and added one of their own. They were classified mainly on a mycotic-embolic or arteriosclerotic basis. In 1948 Scott[2] again reviewed the literature and brought the total number of cases of localized aneurysms of the coronary arteries, including one of their own, to forty-seven. He suggested a reclassification, adding congenital aneurysms and syphilis as causes. He considered some of the arteriosclerotic aneurysms of Packard and Wechsler[1] to be congenital. Of the forty-seven cases reported, they were divided as follows: fifteen congenital, six arteriosclerotic, twelve mycotic-embolic, six syphilitic, four of other types and four unclassified.

Since Scott's[2] paper, two more cases have been reported by Sarkisian[3] in 1950 and Rukstinat[4] in 1952, the etiology being on an arteriosclerotic basis in each case.

Arteriovenous Fistulas of the Coronary Arteries.—The present case showed in addition to the aneurysm of the coronary artery, a large dilated and atherosclerotic vessel communicating with the right atrium. Although this is not regarded as a vein, its connections would result in an arteriovenous shunt.

A few cases of coronary arteriovenous fistula may be cited. Harris[5] describes a case with an aneurysm of the right coronary artery communicating with the right auricle. It is explained as a congenital anomaly probably due to deficiency in elastic tissue. Communication with the auricle is attributed to development of a fetal communication which is ordinarily reduced to capillary size.

Essenberg[6] described a case of anomalous coronary arteries in a 22-week fetus in which a branch of the left coronary artery entered the wall of the left atrium and turned toward the right atrium, the wall of which it entered. He considered that it probably opened into the cavity of the right atrium.

Another peculiar anomaly, an arteriovenous communication between the right coronary artery and the coronary sinus with aneurysmal dilatation of the parts involved was described by Halpert.[7] This condition was an incidental finding at necropsy of an adult man who died of carcinoma of the stomach and who during life showed no clinical evidence suggesting a cardiac defect. Clinical examination of the heart revealed no signs except a systolic murmur at the apex.

In the present case, the histology and the absence of any communication with coronary veins or sinuses strongly suggest that the vessel opening into the right auricle is a congenital abnormality of the coronary arteries and not an abnormal communication, either congenital or acquired, between artery and vein. Moreover, the presence of the aberrant vessel suggests that the aneurysm of the coronary artery is essentially of a congenital type. This lesion caused no apparent disability, but it is possible that the aortic diastolic murmur may have been caused by this lesion, since no apparent incompetence of the aortic valve was seen at necropsy.

SUMMARY

A case of aneurysm of the right coronary artery with an anomalous branch resulting in a functional arteriovenous fistula is described.

The literature has been briefly reviewed and brought up to date, using Scott's classification.

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POSTERIOR VENTRICULAR ANEURYSM IN PATIENT WITH DEXTROCARDIA AND SITUS INVERSUS

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VENTRICULAR aneurysm is found at necropsy in about 10 per cent of the hearts that have sustained myocardial infarction.[1-3] In the past, coronary artery disease has been reported as the cause of approximately 85 per cent of ventricular aneurysms.[4] The decreasing incidence of such other etiologic factors as gumma of the myocardium, abscess of the heart secondary to bacterial endocarditis, rheumatic myocardial necrosis and tuberculosis will undoubtedly cause an even greater proportion in future years. Nearly 80 per cent of ventricular aneurysms involve the anterior wall and apex of the left ventricle, while less than 20 per cent occur at the base of the posterior wall.[5,6] Anterior ventricular aneurysms frequently manifest a characteristic diffuse paradoxical pulsation medial to the cardiac apex,[7] and since they are located in the region where routine precordial electrocardiographic leads are taken, typical electrocardiographic changes are often evident.[1,8,9] The characteristic chest x-ray showing a blunted rectangular appearance of the cardiac apex has also aided in the frequent clinical recognition of anterior ventricular aneurysm. On the other hand, the clinical recognition of posterior ventricular aneurysm during life was first reported by Parkinson and associates[4] in 1938, and only a few reports have appeared in the subsequent literature. The current trend for early surgical attack on unexplained intrathoracic lesions makes it increasingly important to diagnose correctly nonsurgical conditions such as ventricular aneurysm so that these patients will be spared needless surgical procedures. It is the purpose of this paper to report such a case. Our patient had an exploratory thoracotomy in 1949 for "possible malignancy or pericardial cyst." He had dextrocardia with complete situs inversus, and failure to reverse properly the limb leads of the electrocardiogram or to take unipolar leads over the posterior aspect of the right chest resulted in tracings which failed to reveal the characteristic electrocardiographic changes of old posterior myocardial infarction prior to surgical exploration.

CASE REPORT

A 37-year-old Negro soldier was admitted to Madigan Army Hospital on July 25, 1952, because of dyspnea on exertion and recurrent pain beneath the right scapula. He had known he had dextrocardia since 1943. He enjoyed excellent health until 1946, at which time he had a severe illness characterized by sudden pain just inferior to the right scapula with considerable associated shortness of breath. He was hospitalized in an overseas military hospital for a total of three months but was unaware of the diagnosis. (The medical records of this hospitalization are

From the Medical Service of Madigan Army Hospital, Tacoma, Wash.
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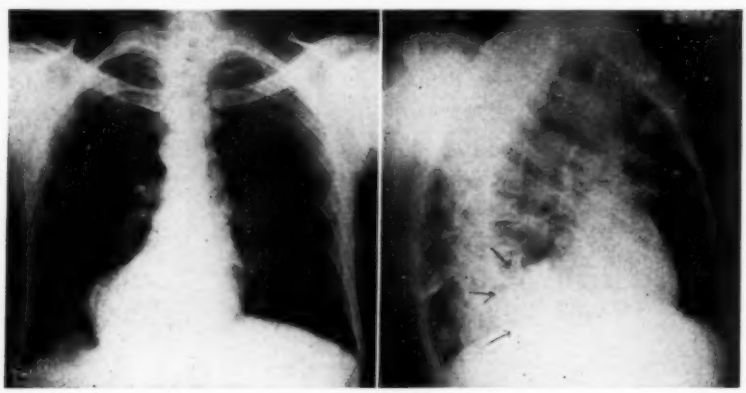
not available.) After return to duty, he continued to have moderate dyspnea and dull pain beneath the right scapula, both of which were aggravated by exertion. He had experienced episodes of paroxysmal palpitation with cardiac irregularity. These had always disappeared without treatment. In July, 1949, he was hospitalized at a military hospital in the United States for tonsillectomy. At this time he was found to have a positive blood serology and was treated with 6,000,000 units of penicillin. A routine chest x-ray showed an unusual cardiac shadow which was thought to indicate a pericardial cyst. Subsequent studies demonstrated a rounded mass 7 cm. in diameter which appeared continuous with the posterior lateral aspect of the heart. Electrokymographic studies were performed and the results were interpreted as showing early movement of the mass opposite in direction to ventricular motion. The impression was ventricular aneurysm.



A. *B.*

Fig. 1.—*A*, Posterior anterior chest film which shows dextrocardia with broadening and blunting of the cardiac apex; this gives the heart a square or rectangular appearance characteristic of ventricular aneurysm. *B*, Right oblique projection, the aneurysm projects backward and its upper margin forms a typical ledge or shelf-like projection from the wall of the ventricle.

Angiocardiography, however, failed to show evidence of opacification or filling of the spherical mass posterior to "the right sided left ventricle." (Shepard and Steward[10] have suggested that in place of right and left ventricle one use the term "systemic" and "pulmonic" ventricle in describing patients with dextrocardia.) The electrocardiogram was reported to show abnormal T-wave changes of a nonspecific type. As previously stated subsequent review of these tracings indicated that lead wires had not been reversed in order to produce a conventional electrocardiographic pattern and unipolar leads were not taken from the right posterior chest. Because the mass failed to fill at the time of angiocardiography, a thoracotomy was done to rule out a pericardial cyst or intrathoracic tumor. At surgery complete situs inversus was confirmed, the right lung had two lobes and a lingula. A large pulsating mass arose from the posterior aspect of the base of the ventricle. All aspects of the mass demonstrated expansile pulsation synchronous with ventricular systole. The cardiac contractions were regular and forceful. A diagnosis of ventricular aneurysm was made. The patient tolerated the operative procedure well. He made a rapid recovery, and, since he was at that time asymptomatic and without evidence of myocardial dysfunction, he was returned to duty. He continued military duty for the following three years, during which time he had noted increasing dyspnea, right posterior chest pain, and cardiac arrhythmia but had not sought medical aid. Physical examination in July, 1952, revealed a 6 ft. 1 in., 170 pound Negro in no acute distress. He appeared to be the stated age of 37. There was a 30 cm. well-healed right thoracotomy scar. The heart was on the right with the point of maximum impulse in the sixth intercostal space, 8 cm. to the right of the midsternal line. Heart sounds were normal. A Grade 2 apical systolic murmur was heard. The blood pressure was 132/92 mm. Hg. The lung fields were clear. Liver dullness was demonstrated on the left. The remainder of the physical examination was normal.

Laboratory work: White blood count, 6,450, with a normal differential; hematocrit, 48; urinalysis normal with a specific gravity of 1.013. Cardiolipin microflocculation test doubtful; Wassermann, negative. Cardiac fluoroscopy revealed dextrocardia with situs inversus. A large mass protruded from the posterior aspect of the systemic ventricle displacing the barium-filled

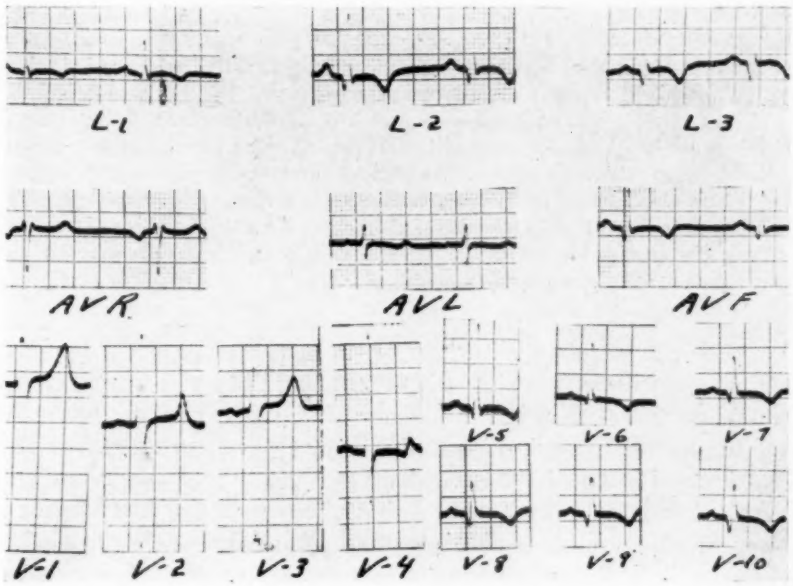


Fig. 2.—Electrocardiogram taken with Lead I reversed and foot lead on right. Precordial leads were taken from the right chest and include leads from the posterior aspects as well.

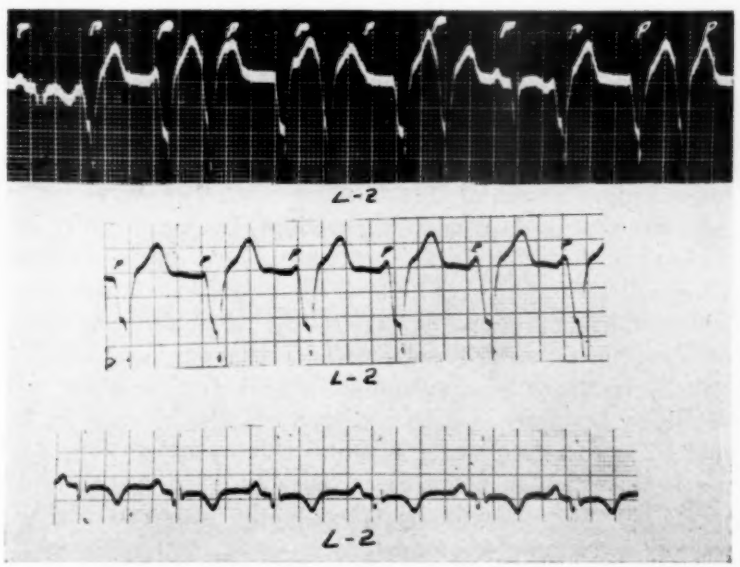


Fig. 3.—*A*, Complex ventricular arrhythmia with two separate parasystolic foci producing ventricular complexes of slightly different form. There is gross irregularity of succeeding beats but alternate beats are completely regular. The first ventricular contraction arises through a normal sinus mechanism while the ninth is a characteristic fusion beat. *B*, Tracing taken after patient had received 1 Gm. quinidine sulfate during a five-hour period. There is an idioventricular rhythm with atrioventricular dissociation. *C*, Reversion to normal sinus rhythm.

esophagus to the posterior and to the left. This mass demonstrated paradoxical pulsation as compared with the cardiac apex (Fig. 1). Electrocardiogram taken with Lead I reversed and the lower extremity lead on the right foot showed broad Q waves in Leads II, III and aV_F. Broad Q waves were also present over the posterior aspect of the right chest but elevation of the S-T segments often evident over ventricular aneurysms was not demonstrated. The changes were considered characteristic of old posterior myocardial infarction (Fig. 2).

Course in the hospital: Patient was asymptomatic except for dull aching pain in the posterior right chest. While in the hospital he developed a most unusual paroxysmal ventricular tachycardia in which two closely related parasystolic foci discharged alternately. As a result there was gross cardiac irregularity of subsequent ventricular beats, but alternate beats were perfectly regular in relation to one another. In addition the auricles continued to discharge at a separate rate. Periodically this would occur when the ventricles were in a responsive state producing interference dissociation and an occasional fusion beat. Following the administration of quinidine sulfate this arrhythmia changed to idioventricular rhythm with complete atrioventricular dissociation and finally reverted to normal sinus rhythm (Fig. 3).

DISCUSSION

Ventricular aneurysms are usually encountered in areas where a large myocardial infarction has occurred with resulting cicatrization and aneurysmal bulging of the fibrosed myocardial wall. They often develop rather soon after myocardial infarction and have been observed as promptly as two days later.[11] Subjecting the heart to unusual stress during the early stage of infarction appears to be an important causal factor in their production. Strenuous physical activity, sustained systemic hypertension or anatomic deformity of the heart valves is the usual source of such stress. In eight of ten cases reported by Dressler and Pfeiffer[7] the nature of the acute myocardial infarction had not been recognized and the patients had not been placed at rest during this crucial time. In twenty cases reported by Moyer and Hiller[12] only three were known to have had adequate rest following infarction and several were cases of "silent" infarction. Experimental results reported by Sutton and Davis[13] also lend support to the view that stress in the immediate postinfarction period is an important factor in the genesis of ventricular aneurysm. After preliminary training on a motor-driven treadmill, the anterior descending branch of the left coronary artery of five dogs was ligated. Exercise was resumed two days later in two dogs, three days later in two dogs, and six days later in the other dog. Exercise was continued for periods varying between 70 and 390 days when each animal was autopsied. It was found that the heart of the dog which was rested for six days had a small, firm, well-contracted scar without thinning of the ventricular wall. In the dogs exercised within three days after the production of myocardial infarction, thin scars with definite aneurysmal bulging occurred in each instance. Except during the acute phase of myocardial infarction rupture of a ventricular aneurysm is extremely rare. In differentiating ventricular aneurysms from pericardial cysts and other intrathoracic lesions advantage should be taken of the fact that patients with an aneurysm usually have sustained an extensive myocardial infarction. A careful review of the history will often elicit a story strongly suggestive of a previously unrecognized myocardial infarction and the electrocardiogram will almost invariably show evidence of such an infarction in the area in question. On the other hand, failure to verify the presence of extensive myocardial infarction by the electrocardiogram in the presence of abnormal bulges on the cardiac silhouette

by roentgenographic study does not exclude, but should cast serious doubt, on the diagnosis of ventricular aneurysm.

Recent reports would indicate that, because of the more frequent occurrence of mural thrombi and the consequent greater incidence of thrombo-embolic phenomena, ventricular aneurysm carries a poorer prognosis statistically than does myocardial infarction without aneurysm.[11] This would suggest that such patients should be observed carefully for evidence of embolic complications and perhaps receive prolonged anticoagulant therapy should these complications occur. The aneurysm is frequently filled with a large laminated thrombus, and this may explain why this patient's aneurysmal sac was not visualized by angiocardiography.

SUMMARY

1. A case of posterior ventricular aneurysm in a patient with dextrocardia and situs inversus is reported.

2. The patient had surgical exploration three years previously for possible pericardial cyst or intrathoracic tumor. Preoperatively it was not recognized that the patient had sustained an old posterior myocardial infarction.

3. The importance of electrocardiographic evidence of extensive myocardial infarction as a valuable aid in differentiating ventricular aneurysm from pericardial and other intrathoracic tumors located against the left ventricle is emphasized.

4. The patient manifested an unusual cardiac arrhythmia with impulses arising from two separate parasystolic ventricular foci.

The authors wish to thank Dr. Harold D. Levine for reviewing the electrocardiograms.

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AURICULAR TACHYCARDIA WITH WENCKEBACH PHENOMENON OCCURRING DURING THE COURSE OF CARDIAC CATHETERIZATION

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THE occurrence of progressively lengthening auriculoventricular block during the course of auricular flutter and the mechanisms involved therein have received sporadic attention in the literature. In a detailed study of A-V conduction in auricular flutter, Besoin-Santander and associates[1] clearly delineated Wenckebach periods in one-half of the records of auricular flutter which showed an irregular ventricular response. Cloetens and Brandes[2] have also reported a case of auricular flutter with Wenckebach phenomenon occurring in an 88-year-old woman with arteriosclerotic heart disease, and Laake[3] described a similar occurrence in a 29-year-old woman without evident organic heart disease. Friedberg and Rothberger[4] have previously pointed out the association of auricular flutter with Wenckebach periods, and Decherd and associates[5] also reviewed the subject of auriculoventricular block associated with paroxysmal auricular tachycardia.

We have recently observed a case of rapid auricular rhythm with periods of Wenckebach phenomenon occurring during the course of cardiac catheterization in a 9-year-old girl with cyanotic congenital cardiac disease, and we were aided considerably in diagnosing the particular arrhythmia present by the use of an intracardiac electrocardiogram and direct auricular pressure tracings. In several large series of electrocardiograms observed during cardiac catheterization, a 6 per cent incidence of auricular flutter has been reported[6] as well as a 2 per cent incidence of partial A-V block,[7] and a 3 per cent incidence of paroxysmal auricular tachycardia.[8] However, there has been, to our knowledge, no prior report of rapid auricular rhythm with periods of Wenckebach phenomenon occurring during cardiac catheterization nor has this particular arrhythmia been previously reported in children this young. The rarity of this finding is particularly interesting since Hoyer and Lyon[9] have emphasized the occurrence of A-V block in the presence of auricular flutter in children. Zimdahl[10] has, however, reported a transient period of Wenckebach phenomenon with slow auricular rate, occurring the third day after cardiac catheterization in a 4-year-old patient who developed complete heart block on the day following catheterization.

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CASE REPORT

The patient, a 9-year-old Negro girl, had a heart murmur first detected at the age of two months. Since that time, her mother noted that she had never been as "lively" as other children, that she fatigued easily and showed dyspnea and squatting when subjected to mild exertion. Her exercise tolerance was very poor and on many occasions she had to be carried after walking only one block. There were also occasional episodes of fainting. Cyanosis was not noted when she was an infant, but her mother had observed blueness of her nail beds during the two years prior to admission.

Physical examination revealed a blood pressure of 110/80 mm. Hg in both arms. The femoral pulses were strong and equal. There were marked clubbing and cyanosis of the fingers and toes. There was a slight precordial bulge. The apex beat was just to the left of the mid-clavicular line in the fifth left intercostal space. There was a harsh, high-pitched Grade 3 systolic murmur heard best at the second left intercostal space, well transmitted over the precordium and into the neck. There was no diastolic component and no thrill was elicited. The pulmonic second sound was greater than the aortic second sound. The lungs were normal.

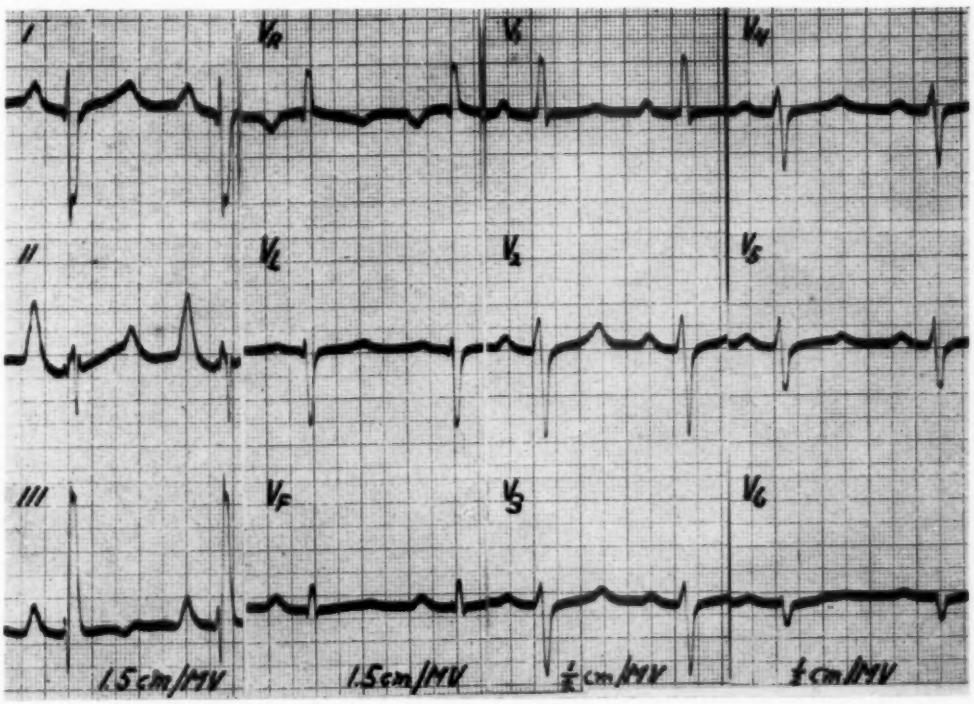

Fig. 1.—Represents the patient's electrocardiogram prior to cardiac catheterization showing a regular sinus rhythm and a constant P-R interval of 0.16 sec. The pattern of right ventricular hypertrophy is present. (Electrocardiogram recorded at twice the usual speed.)

On fluoroscopy, the heart appeared enlarged to the left in the posteroanterior view and the apex was elevated. In the right anterior oblique view, there was encroachment on the retrosternal space anteriorly, suggesting right ventricular hypertrophy. The pulmonary artery segment appeared normal, but the pulmonary vascular markings were sparse. The aortic arch was on the left side.

Hemoglobin was 19.9 grams, the red blood cell count, 8.1 million per cubic millimeter. The white blood count was 7,750 with a normal differential. A vectorcardiogram and an electrocardiogram both showed right ventricular hypertrophy. The initial electrocardiogram (Fig. 1) showed regular sinus rhythm at a rate of 96 with a constant P-R interval of 0.16 sec.

Cardiac catheterization was performed under general anesthesia. The patient was premedicated with 0.4 mg. of atropine sulfate given subcutaneously about one hour before the start of the catheterization and four hours before the onset of the arrhythmia described subsequently. Rectal Avertin was administered in a dosage of 2.8 Gm. (100 mg./kg.) supplemented by local

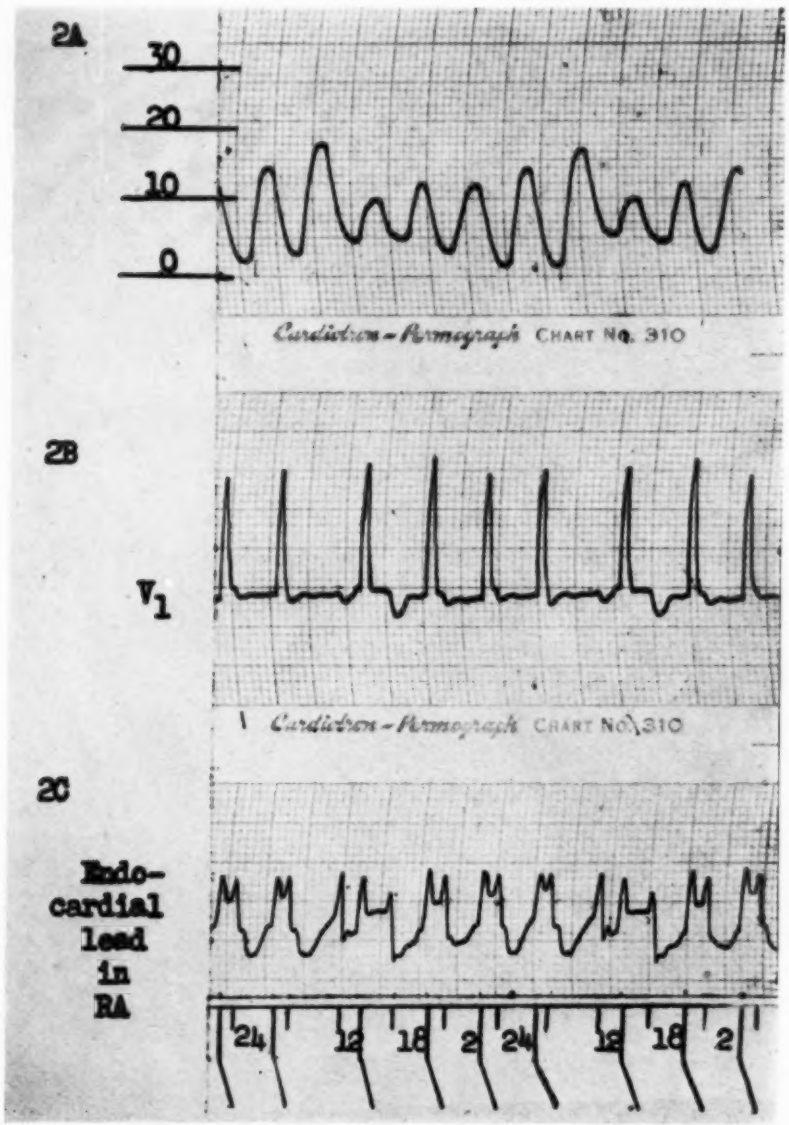

Fig. 2.—*A*, An atrial pressure tracing, with "a-waves" or "flutter" waves occurring in rapid succession, corresponding with the P waves of the endocardial electrocardiogram. The scale is in millimeters of mercury. *B*, represents a simultaneously recorded Lead V_1 showing the same rhythm but in which the P waves are difficult to delineate. *C*, An endocardial electrocardiogram taken with the catheter tip in the mid-right atrium. Each P wave stands out as a biphasic deflection and is designated by a short vertical line in the legend below the electrocardiogram. The gradually increasing P-R interval with eventually a "dropped" beat is clearly evident. The auricular rhythm is regular at a rate of 222 per minute; the ventricular response is irregular at a rate of 174 per minute.

2 per cent procaine and Pentothal Sodium injected into the catheter as needed during the course of the procedure, in a total dosage of 0.375 mg. A No. 7 electrode catheter was introduced into a vein in the left antecubital fossa and advanced into the superior vena cava, right atrium, and right ventricle. The catheter then entered the aorta which seemed markedly deviated to the right. Repeated attempts to enter the pulmonary artery were unsuccessful, the catheter re-entering the aorta on each occasion and at one time passing inferiorly into what was taken to be the descending aorta.

During the course of the catheterization, with the tip of the catheter in the mid-right ventricle, 5 c.c. of Evans Blue dye were injected into the catheter and a right ventricle-to-ear circulation time determined by ear oximetry according to the method of Lasser and associates.[11] The catheter again entered the aorta, was pulled back into the right ventricle, and then withdrawn into the mid-right atrium. At this time it was noted that the patient had extremely rapid heart action with transition from a sinus tachycardia with a rate of 140 to a supraventricular tachycardia at a rate of 215. Rapid auricular rhythm with periods of Wenckebach phenomenon then ensued as depicted in Fig. 2. In this figure, the P waves are clearly delineated in the endocardial lead (Fig. 2,*C*) and stand out as biphasic deflections as seen in direct leads taken from the mid-right atrium.[12] The auricular rhythm is regular with a rate of 222 per minute and the ventricular response is irregular with a rate of 174 per minute. From the legend, one notes in general a 1:1 rhythm with a gradually increasing P-R interval and a "dropped" ventricular beat after every fifth P wave, the Wenckebach phenomenon being clearly evident. Fig. 2,*B* represents a simultaneously recorded Lead V_1, showing the same rhythm but in which the P waves are more difficult to delineate. Fig. 2,*A* is an atrial pressure tracing with "a-waves" or "flutter" waves occurring in rapid succession, corresponding with the P waves of the endocardial electrocardiogram.

With the onset of this arrhythmia, the patient was treated by administration of oxygen by mask and a total dose of 0.6 mg. of Cedilanid injected into the catheter in two doses given ten minutes apart. Carotid sinus pressure produced no immediate alteration of the cardiac rhythm. The catheter was temporarily withdrawn from the atrium during the arrhythmia but was later reinserted. Within thirty minutes the rhythm reverted abruptly to a sinus tachycardia of 140 and this remained throughout the rest of the procedure. However, severe hyperpnea with a respiratory rate of 40 per minute ensued and the patient remained only slightly responsive to noxious stimuli despite the fact that no further anesthesia was given and the level of anesthesia was felt to be quite "light" at the time. There were no focal neurologic signs, and there was no evidence of congestive heart failure to explain the hyperpnea, the lungs remaining clear. The mental clouding and hyperpnea continued despite restoration to sinus rhythm and administration of oxygen. However, these symptoms gradually subsided upon the patient's return to the ward and six hours after the onset of the arrhythmia, the hyperpnea was no longer evident, the patient was alert, and the heart showed a sinus rhythm at a rate of 100.

A blood specimen taken from a position high in the right atrium (not in the region of the coronary sinus) shortly after the onset of the auricular tachycardia was considerably unsaturated, showing an oxygen content of 2.2 volume per cent and a saturation of 8.3 per cent, reflecting the great degree of anoxia present in the patient at that time. As compared with this, a specimen from the right ventricle taken prior to the onset of the arrhythmia showed an oxygen content of 16.86 volume per cent with a saturation of 62.6 per cent. Right ventricular pressure was elevated to 110 to 140/0 mm. Hg. Aortic and femoral artery systolic pressures were almost identical to that in the right ventricle, 100-110 mm. Hg, a finding consistent with the presence of overriding of the aorta. Peripheral arterial oxygen saturation (taken prior to onset of arrhythmia) was diminished, showing a value of 69.1 per cent. Inasmuch as this patient probably has a Tetralogy of Fallot (although this was not definitely established by catheterization as the pulmonary artery was not entered), the right ventricular and right atrial oxygen contents may not be expected to be the same because of the presence of an interventricular septal defect, possibly with a left-to-right shunt, raising the oxygen concentration in the right ventricle. The difference between the oxygen content in the blood drawn from the two chambers is probably too great, however, to be explained solely by the presence of a left-to-right shunt into the right ventricle.

DISCUSSION

The differentiation between auricular flutter and auricular tachycardia may be impossible by electrocardiographic means, and since they may actually be manifestations of the same process,[13] we have preferred to call our case an example of a rapid auricular rhythm without further definition, rather than to attempt to differentiate as to which of the two conditions occurred in this case. In view of the auricular rate below 250, the abrupt return to normal sinus rhythm following digitalis administration and the predominantly 1:1 A-V ratio, the older criteria for the existence of auricular tachycardia as opposed to auricular flutter, are at least partially fulfilled.[14,15]

The mechanism of occurrence of rapid auricular rhythm with the Wenckebach phenomenon has received rather detailed investigation through the years and, inasmuch as it has not previously been reported during cardiac catheterization, it is interesting to speculate as to the possible underlying factors which caused it in this case. Direct mechanical teasing of the auricular wall in dogs and mild stimulation in human beings has resulted in the production of auricular paroxysmal tachycardia[13] and the occurrence of rapid auricular rhythm during cardiac catheterization is well established. Mechanical stimulation from the catheter may produce not only functional disturbances as manifested by arrhythmias, but also traumatic organic lesions. Edwards and his associates[16] have demonstrated such lesions in two of twenty-eight cases examined post mortem, one case showing a small focus of hemorrhage in the right atrium. Banfield and associates[17] and Ellis and associates[18] have also reported mural thrombi and subendocardial necrosis and hemorrhage in the atria of catheterized dogs and Sancetta and associates[19] have demonstrated subendocardial right atrial hemorrhage in a catheterized man. In the case under discussion, however, the situation is much more complex and while mechanical irritation of the atrium may have been one factor involved in the production of the rapid auricular rhythm with Wenckebach phenomenon, the factors of hypoxia, vagal stimulation or inhibition and administration of anesthetic agents all may have been involved. In considering the interrelation of these factors, it is difficult to separate one from the others and to incriminate it as the sole, or even the major, cause of the arrhythmia. Studies of arrhythmias occurring during cardiac surgery[20,21] have actually indicted all of the factors previously mentioned but separating one from the other has proved difficult.

The influence of rapid auricular rate, of itself, upon the conducting tissue of the A-V node has been pointed out by Lewis and Master[22] and emphasized by Decherd and Ruskin,[23] who observed dropped auricular beats occurring in response to rapid auricular action and felt that the power of the A-V node to conduct decreased progressively during the period of rapid beating. With the decline in conductivity of the A-V nodal tissue, the auricular impulse reaches the node before it becomes responsive and hence prolongation of the P-R interval and finally dropped beats (i.e., the Wenckebach phenomenon) may occur. This factor of rapid auricular rate may also be associated with a varying extent of penetration of nonconducted auricular impulses resulting from variations of the

refractory periods of the tissues of the A-V node.[1] In addition, vagal stimulation and hypoxia may also lengthen the recovery period.[22] Decherd and Ruskin alluded to the complexity of determining the exact etiology of the Wenckebach type of A-V block by pointing out that, although increased vagal tone shifts the recovery curve in the direction of greater A-V block and slower recovery, the slower auricular rate associated with this may allow for more complete recovery. However, it would appear that under the influence of vagal stimulation A-V block tends to develop at lower auricular rates than normally[13,22] and Prinzmetal and associates[13] attribute the existence of varying degrees of A-V block in auricular flutter, at least in part, to varying vagal tone, which in turn alters the conductivity of the A-V node.

The influence of the autonomic nervous system on A-V conduction might have some importance in discussing the etiology of the Wenckebach block occurring in this patient, as atropine was administered prior to catheterization. Wenckebach periods have been produced experimentally in the frog's heart by repeated vagal stimulation[24] and administration of atropine to a human has resulted in reversion of Wenckebach periods to normal conduction.[25]

Although one should expect atropine to diminish the tendency to develop the Wenckebach type of A-V block because of its neutralization of vagal effect, actually attacks of paroxysmal auricular tachycardia have been precipitated by atropine[26] and, in an unusual case reported by Fine and Miller,[27] vagal inhibition was suspected of causing an incomplete A-V block with Wenckebach phenomenon. In this case, the authors noted the onset of short runs of paroxysmal auricular tachycardia with incomplete A-V block and Wenckebach periods occurring only when the patient assumed a sitting or standing position, normal sinus rhythm being restored when the patient was recumbent. The authors attributed the onset of normal sinus rhythm in the recumbent position to an increase in vagal tone resulting from a stimulation of vagal centers associated with an increase in blood flow to the head. They felt that the upright position caused a tendency to massing of blood in the splanchnic area and lower extremities and hence a lessening of vagal tone. The correctness of these suppositions may be open to question, however. At any rate, the mechanism of the seemingly anomalous occurrence of paroxysmal auricular tachycardia with Wenckebach periods following atropine administration may perhaps be associated with a rapid auricular rate, which, as pointed out, in itself may increase the refractory period of the A-V node. It is known that carotid sinus stimulation may be ineffective in very rapid auricular paroxysmal tachycardia or auricular flutter and may only be successful at slower auricular rates.[13]

The marked hypoxia noted in our patient may also be taken into consideration in discussing the etiologic factors involved in the production of her arrhythmia. Anoxia has long been accepted as one of the factors which decreases the conductivity and increases the refractory period of the A-V nodal tissue,[13,22,23] and hence would favor the development of A-V block. One mechanism proposed was that the metabolic products of the asphyxiated state were toxic to the A-V conducting tissue,[22] preventing it from functioning properly. More recently, however, it has been noted that hypoxia potentiates vagal action or acetylcholine[28]

and this, in turn, would tend to cause the production of increasing A-V block. However, oxygen administration has no apparent effect on A-V conduction time in patients with heart block and an apparently normal oxygen saturation.[29] Whether the hypoxia precipitated or, as is more likely, was the result of the arrhythmia in our patient, its existence undoubtedly aggravated the situation and quite possibly prolonged the arrhythmia.

Digitalis promptly restored our patient to normal sinus rhythm, although it should be realized that, concomitant with digitalis administration, the possible irritating influence of the catheter was removed and oxygen was administered in an attempt to correct the ill effects of hypoxia. Digitalis has classically been known to increase the refractory period of the A-V conduction system and in fact, the usual occurrence of the Wenckebach type of A-V block has been associated with digitalis toxicity.

In a review of forty cases of paroxysmal auricular tachycardia with A-V block, twenty-two of whom had block of the Wenckebach type, only seven patients had received no digitalis prior to the onset of the arrhythmia and over one-half had obvious digitalis overdosage.[5] In a patient with paroxysmal auricular tachycardia, administration of Digoxin has been felt to have precipitated a Wenckebach type of A-V block.[30] Whether the apparent success of digitalis in terminating the abnormal rhythm in this case was due to its direct effect in diminishing the excitability of the auricle and hence slowing its rate (in distinction to its vagal effect which presumably would tend to perpetuate or increase the existing A-V block), or whether the adjuvant measures employed were the most important factors is difficult to state. It is felt that all the abnormal factors mentioned should be corrected, if possible, in order to restore the rhythm to normal. The importance of auricular rate as a factor, however, may be well seen in our case, as this patient developed the Wenckebach type of A-V block only after the prior existence of a supraventricular tachycardia with normal A-V conduction.

SUMMARY

1. A case is presented of rapid auricular rhythm with Wenckebach type of A-V block occurring during the course of cardiac catheterization in a 9-year-old girl with congenital cyanotic heart disease.

2. The aid of intracardiac leads and pressure tracings from the right atrium in establishing the nature of the arrhythmia is demonstrated.

3. The various factors influencing the development of the Wenckebach phenomenon are discussed with particular emphasis on the influence of the autonomic nervous system, auricular rate, hypoxia, and digitalis, and it is seen that attention to all of the factors involved may bring about rapid reversion to normal rhythm.

Appreciation is expressed to Dr. Arthur Grishman and Dr. Simon Dack of the Cardiographic Department of The Mount Sinai Hospital, New York, for their aid in reviewing the electrocardiographic records in this case.

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SUPERIOR VENA CAVA OBSTRUCTION WITH COMPLETE OBSTRUCTION OF THE RIGHT MAIN PULMONARY ARTERY

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REPORTS concerning superior vena cava obstruction are not uncommon. Calenda and Uricchio were able to document a total of 567 reported cases.[1] Occlusion of a main pulmonary artery is distinctly unusual. We are unaware of any report of a combination of the two. We have recently studied such a case and consider it worthy of documentation.

CASE REPORT

A 30-year-old Negro male was first admitted to Fitzsimons Army Hospital on Feb. 10, 1953, with the history that on Sept. 10, 1950, he had been blown from a foxhole in Korea by the explosion of an enemy concussion grenade. He was not rendered unconscious but immediately coughed up one to two tablespoonfuls of bright red blood. He continued to cough up streaks of bright red blood and bits of clotted blood for the next 18 to 24 hours. A chest roentgenogram was not taken at this time. The patient was treated at a forward installation for a period of 72 hours and then returned to the front line. He was asymptomatic at the time of his return to duty. On Sept. 22, 1950, the patient received multiple, superficial, shell fragment wounds of the lower extremities and one small fragment lodged superficially in the posterior chest wall. No penetrating chest wound was received. The patient had no residuals from these wounds and considered himself in excellent health until Jan. 7, 1953, when a routine posteroanterior chest roentgenogram demonstrated a linear and nodular infiltration in the right upper lung field; for this reason the patient was hospitalized at Fitzsimons Army Hospital.

At the time of admission to the hospital the patient denied any past or present symptoms suggestive of tuberculosis or any other type of pulmonary infection or disease except for the above mentioned episode. Physical examination was entirely normal except for a contracted right hemithorax, with decreased expansion and decreased excursion of the right leaf of the diaphragm. There was no evidence of superficial venous distention in the head, neck, upper extremities, or the upper trunk. White blood count, erythrocyte sedimentation rate, hemoglobin, and urinalyses were normal at the time of admission and remained so throughout his hospitalization. The first strength tuberculin skin test (purified protein derivative) was 3 plus. Histoplasmin skin test was 1 plus in a 1:1,000 dilution. Coccidioidin skin test was negative in both 1:1,000 and 1:100 dilutions. Ten sputum cultures, 4 gastric cultures, and 2 bronchoscopic aspiration cultures were all negative for acid fast bacilli and pathogenic fungi. Complement fixation tests performed on March 20, 1953, were negative for *Coccidioides immitis*, *Histoplasma capsulatum*, and *Blastomyces*. Bronchoscopy performed on March 13, 1953, showed a fish mouth deformity suggestive

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Fig. 1.—Posteroanterior roentgenogram showing contracture of right hemithorax and fibrosis of right lung.

Fig. 2.

Fig. 3.

Fig. 2.—Posteroanterior angiogram showing no dye entering heart.

Fig. 3.—Oblique angiogram showing venous drainage by retrograde flow through internal mammary, azygos, and superior intercostal veins.

of extrinsic pressure on the bronchus of the right upper lobe. The patient was considered a diagnostic problem from the beginning of hospitalization, but because of the pulmonary parenchymal infiltration revealed by chest roentgenogram, the positive tuberculin skin test, and the patient's race, he was started on para-amino-salicylic acid, 12 Gm. daily, and Streptomycin, 2 Gm. every third day, on March 16, 1953. Isonicotinic acid hydrazide, 300 mg. daily, was substituted for the para-amino-salicylic acid on June 24, 1953. Chemotherapy was discontinued

Fig. 4.—Angiocardiogram demonstrating complete obstruction of right pulmonary artery.

on Oct. 29, 1953. Internal bronchospirometric examinations performed on Oct. 19, 1953, gave the following readings for the right lung: vital capacity, 900 c.c.; tidal air, 800 c.c.; ventilation, 3,650 c.c. per minute; oxygen consumption, zero. An electrocardiogram on Oct. 20, 1953, was normal. Chest roentgenograms showed no change between admission and the roentgenogram taken on Oct. 21, 1953 (Fig. 1). Previous chest roentgenograms were not available for comparison. Venous pressures by the direct method revealed 270 mm. of water in both antecubital veins and 150 mm. of water in the saphenous vein. The arm-to-tongue circulation time (Decholin) was 13.5 seconds in the right arm and 14.2 seconds in the left arm. Angiocardiography was attempted on Oct. 29, 1953 with 50 c.c. of dye (Urokon) injected in the right antecubital vein with ease. The resultant angiogram showed no dye entering the heart from the superior vena cava but demonstrated a large collateral circulation by retrograde flow through the internal mammary and azygos venous systems (Fig. 2 and 3). Angiocardiography was then performed through a tributary of the right femoral vein. This study clearly demonstrated complete occlusion of the right main pulmonary artery (Fig. 4).

DISCUSSION

It is believed this man suffered a concussion injury of the chest with hemorrhage into the right hilar structures at the time of his initial injury. The resulting fibrosis and contraction occluded his superior vena cava, the orifice of the azygos, and has also occluded the right pulmonary artery.

The symptoms of superior vena cava obstruction are typically dyspnea, cough, headaches, chest pain, hoarseness, dysphagia, drowsiness, convulsions, and facial pain.[2,3] The physical signs are cyanosis, edema of the face, neck, upper extremities, and upper trunk, and venous distention. The degree of visible collateral venous circulation depends upon the location of the obstruction. The experimental work of Carlson[4] and clinical observations of others indicate that the relationship of the obstruction to the opening of the azygos is of primary importance.[2,3] When the obstruction is above the azygos the flow of blood in the azygos is in a normal direction and venous drainage of the superior venal caval field will depend to a great extent on superficial and, therefore, visible venous collaterals. If obstruction occurs below the azygos orifice the blood empties directly into the azygos from the superior vena cava and by retrograde flow eventually into the inferior vena cava. In this situation visible collaterals may not develop. If the orifice of the azygos is obstructed, the azygos may diminish in size and collateral venous drainage will develop in the more superficial systems, or the azygos may become an important collateral aid in draining blood into the inferior vena cava. In this situation the superior intercostal vessel becomes an important collateral connecting with the azygos at the most cephalad portion of the azygos.[5] The angiograms in our case clearly demonstrate the superior intercostal entering the azygos.

It is worthy of note that our case is completely asymptomatic and shows none of the physical signs associated with superior vena cava obstruction. Our case demonstrates an elevated venous pressure but normal circulation time.

Savacool and Charr[6] in a review of the literature reported 100 cases of thrombosis of one or both branches of the main pulmonary artery; the chief clinical features were dyspnea, cyanosis, chest pain, restlessness, and confusion.

According to Davis and co-workers, when one main pulmonary artery is permanently occluded, the corresponding lung becomes reduced in size and a fibrosis occurs about the alveolar walls and about the bronchiovascular tree.[7] The present case demonstrates such findings by physical examination and chest roentgenography.

Bloomer and co-workers[8] have shown experimentally that following complete occlusion of a main pulmonary artery the bronchial artery can assume a certain amount of respiratory function.

SUMMARY

A case of complete obstruction of the superior vena cava and right main pulmonary artery secondary to a concussion injury is reported. The patient is completely asymptomatic with no visible venous collaterals.

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Review of Recent Advances

THE ANOXEMIA TEST

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INTRODUCTION

ANGINA pectoris as a manifestation of coronary insufficiency is the most common cause of substernal and precordial distress in those individuals in the middle and late decades of life. In many instances this association and diagnosis can be readily established. In others, however, the appraisal of substernal and precordial pain may be difficult. The findings that electrocardiographic alterations may be induced in certain patients by breathing lower amounts of oxygen than occur in ordinary air (the so-called anoxemia test of Levy) and may also be induced if patients exercise (the so-called exercise test of Masters) have been used to give objectivity to the subjective complaint of pain. The clinical tests which arose from these observations frequently aid in the establishment of the diagnosis of coronary insufficiency. The exercise test has been the subject of recent review by Scherf and Schaffer.[90] It is the purpose of this review to consider the experience in the use of the anoxemia test, to summarize the present status of opinions about the test, and to appraise its areas of usefulness.

The anoxemia test was designed to provide objective evidence of the presence of coronary insufficiency. The diagnosis of angina may be readily made in patients who have the typical symptoms of angina, in whom pain is relieved promptly by nitroglycerine. In these the diagnosis may be further substantiated if there is cardiac enlargement, if the electrocardiogram is abnormal, and if there is a history of previous myocardial infarction. On the other hand, in approximately 25 per cent of patients suffering from typical angina pectoris the electrocardiogram may be normal and the blood pressure and heart size may be within normal limits.[108] In them the diagnosis is in large measure based on the history of pain. In certain other patients the distribution of pain and its occurrence may not be typical. Certain patients do not provide accurate histories, or they vary the accounts of their discomfort. In other instances the history may be warped by the question of the payment of insurance for disability. In such

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patients the availability of an objective test of the adequacy of the coronary circulation would be an invaluable aid in diagnosis. The anoxemia test in certain instances supplies this need.

The anoxemia test is based on the premise that angina pectoris is due to anoxia of the heart muscle. There is evidence for this point of view in the experience that angina occurs with exertion when an increased amount of blood and, in turn, of oxygen, are required by the heart muscle. The amount of blood and, therefore, of oxygen might be adequate during rest, but due to the narrowing of the coronary arteries, a sufficient amount of blood to supply oxygen for the exercise cannot be carried for the requirements of the myocardium. The anoxemia test is based on the observation that patients who suffer angina on exertion may have reproduction of the pain when they breath low concentrations of oxygen which, in turn, results in lowered saturation of the arterial blood with oxygen and makes a reduced concentration of oxygen available to the cardiac muscle cells.

In the anoxemia test the objective signs are the appearance of certain abnormalities in the electrocardiogram on the breathing of low concentrations of oxygen, signs which do not appear in the electrocardiograms of normal subjects or subjects with normal hearts when exposed to the same stress. These changes when marked may resemble those seen in electrocardiograms recorded during spontaneous attacks of angina. In certain patients with typical angina, about which there is no question that they have coronary insufficiency, and in whom the accessory data give weight to the diagnosis, the correlation has been made that breathing a low concentration of oxygen induces changes in the T waves and RS-T segments of the electrocardiogram. In short, the patients have positive anoxemia tests. In a certain number of patients in whom the anoxemia test has been done it has been possible to substantiate the diagnosis of coronary artery disease by autopsy reports. It has also been demonstrated that for the most part normal subjects and patients with normal coronary circulations do not exhibit these electrocardiographic changes on breathing a low concentration of oxygen. The two correlations, one between known coronary artery disease with angina and positive electrocardiographic changes during oxygen deprivation, and the other between absence of coronary artery disease and negative electrocardiographic changes during oxygen deprivation, in a sufficiently large number of patients, provide a basis for the inference that the so-called anoxemia test gives objective evidence for the presence of coronary insufficiency. How well it fulfills the function of providing an objective test of coronary efficiency will be analyzed in this review. Levy and his associates have provided much of the clinical background for the use of this test and have established the criteria which are generally employed.

DEFINITION

The anoxemia test as now performed in clinical practice is a method of evaluation of the efficiency of the coronary circulation by the demonstration of certain changes which may result from the effects of induced anoxia in the myocardium as reflected in the standard four-lead electrocardiogram. These electro-

cardiographic abnormalities are evaluated by criteria, based upon the maximal alterations recorded in control subjects with normal hearts, which have been established from a large series of careful observations.[47-49,52,53] Anoxia is usually produced by inhalation without rebreathing of various standard low oxygen-nitrogen mixtures for an arbitrary period of time or until anginal pain is experienced within that period of time. When electrocardiographic changes of an abnormal or pathologic nature occur, they are like those seen during spontaneous atttacks of angina.[83,92] While the exact mechanism of the initiation of cardiac pain is unknown, it appears that an important factor in its production is myocardial anoxia[37,39-41,88,89,92,93] which in most cases results from coronary artery disease.

HISTORICAL

Basic observations on which the anoxemia test is founded were made by Green and Gilbert[31] in 1921. In twenty-one healthy aviation cadets they demonstrated that extreme anoxia induced changes in the electrocardiogram, these changes being characterized by decreased, isoelectric or inverted T waves. They found also that vasovagal reactions and syncope sometimes occurred. Recovery was rapid on breathing ordinary air. Dietrich and Schwiegk[22] in 1932 using breathing mixtures of 8 per cent oxygen in nitrogen, and also by means of a decompression chamber, demonstrated lowering or inversion of T waves with some RS-T depression in normal subjects, on the one hand, and marked alterations of the RS-T segment with inversion of T waves and occurrence of pain in anginal patients, on the other hand. These changes were reversed when the patients breathed room air. Rothschild and Kissin[88] in 1933 by a rebreathing method induced pain in eighteen of twenty-six anginal patients. Eight of twenty-four patients in whom electrocardiographic studies were made showed RS-T deviations, but they were not of greater magnitude than were seen in some subjects without angina. Katz and Hamburger[37] in 1933, also using a rebreathing method, demonstrated lowering of amplitude of T waves and RS-T depression. They were unable, however, to find significant changes during rebreathing in anginal patients and in some normal subjects. Studies by May[68] in 1939 using a similar method, namely, rebreathing, in normal subjects showed progressive T-wave flattening and occasionally slight RS-T segmental depression. That similar changes could be induced in normal subjects by decrease of atmospheric pressure was shown by Borgard and Koch[16] in 1934, Cluzet and associates[21] in 1935, and by Tigges[103] in 1936. The anoxia induced in the studies, which are now being discussed, resulted from breathing approximately 8 to 10 per cent oxygen. In 1938 carefully controlled and analyzed studies were carried out by Larsen[42] in twenty healthy persons who breathed a mixture of 9 per cent oxygen in nitrogen without rebreathing for periods of from five to eight minutes. He found that the RS-T segmental displacement did not at any time exceed 1.0 mm. in any lead, and that T_1 and T_2 decreased in amplitude or became isoelectric, but that inversion of T_1 or of T_2 was not observed. He made observations also in twenty-four patients with angina. Four of ten patients who exhibited normal resting electrocardiograms had marked electrocardiographic changes during the test

as contrasted with the changes in normal subjects. Five of ten patients who had only slight electrocardiographic abnormalities at rest showed marked T-wave and RS-T segmental changes during the test. In another group of seventeen patients in whom the diagnosis was "coronary angina pectoris" thirteen had abnormal electrocardiographic changes with induced anoxia. Larsen recorded only three standard leads simultaneously. Larsen's paper, written in Danish, has an extensive summary in English. In 1938 Levy and associates[48] using a 12 per cent oxygen in nitrogen mixture showed that T-wave and RS-T segmental changes of considerable degree occurred in seven of ten patients with heart disease in contrast to minor deviations in eight patients without heart disease. Larsen[42] as well as Levy and associates[53] observed that both electrocardiographic changes and pain occurred in some patients, while in other patients electrocardiographic alterations and pain occurred independently. Levy and his associates[48] found that the arterial oxygen saturations varied from 83 to 67 per cent at the end of the test. Subsequently, Levy and associates[49] in 1939 reported a series of 112 tests in 105 patients using a mixture of 10 per cent oxygen and 90 per cent nitrogen. In the absence of significant anemia none of their sixty-six control subjects had positive electrocardiographic tests. On the other hand, all seventeen patients with suspected coronary artery disease had positive electrocardiographic tests. In 1939-1940 Riesman and associates[82,83] pointed out that changes which occurred as a result of anoxemia were similar to those appearing in anginal patients after exercise, and that electrocardiographic changes in the latter test were prevented by inhalation of oxygen. Eight control and five anginal patients were studied. More recent studies will be discussed in the next section.

NORMAL AND ABNORMAL CHANGES IN THE ELECTROCARDIOGRAM WITH ANOXIA

Levy's Criteria for Positive and Negative Anoxemia Tests.—As a consequence of anoxia in normal subjects the electrocardiogram may show increase in heart rate, decrease in amplitude even to the isoelectric level, or inversion of T waves and variable degrees of RS-T segmental displacement, all depending on the degree to which the anoxia is carried.[21,31,37,68,92,93] However, under the conditions prevailing in the anoxemia test as currently carried out without rebreathing, the RS-T displacement in the three standard leads is not usually more than 0.5 mm. in any lead and should not exceed 1.0 mm. in normal subjects.[42,61,102] Although there may be considerable decrease in amplitude of the T waves, complete inversion of T_1 does not occur. Partial inversion of T_1 or T_2 is occasionally seen and complete inversion of T_3 may occur in the absence of significant alteration of the RS-T segments. The changes in the three standard leads and chest Lead IV F—the derivations used by Levy—which are now commonly considered as representing abnormal responses to the anoxemia test were established by Patterson and associates[72] in 1938-42. Levy's criteria for an abnormal response, that is to say, a positive test, are as follows:

1. "The arithmetical sum of the RS-T deviations in all four leads (I, II, III, and IV F) totals three millimeters or more.

2. There is partial or complete reversal of the direction of the T wave in Lead I accompanied by an RS-T deviation of 1 mm. or more in this lead.

3. There is complete reversal of the direction of T in Lead IV F, regardless of the RS-T deviation."

Levy's criteria were based on observations made on 115 apparently normal persons (whose ages ranged from 21 to 78 years), and on studies carried out in 147 patients with heart disease. These criteria have been accepted both in the United States and abroad. Although they are based on and refer strictly to the anoxemia test as performed by Levy and associates,[53] they have been found from experience to apply for the most part to tests done in slightly different ways by many observers throughout the world. Some observers have used twelve electrocardiographic leads, namely, the three standard, the three unipolar limb leads, and six precordial leads instead of the three standard leads and chest Lead IV F.[70,102,104] It does not appear, however, that the taking of twelve derivations has significantly improved the evaluation of normal and abnormal responses to anoxia. It is a fact that the most striking changes may occur in any of the left percordial leads. It has been suggested by Turner and Morton[104] that a displacement of the RS-T segment of more than 2 mm. in the chest lead is, in most instances, regarded as significant. The changes which occur as a consequence of anoxemia are like those found by Bayley and associates[6] in experimental animals, in which the alterations were attributed to subendocardial ischemia. The electrocardiographic abnormalities were quickly dispelled by the abolition of the anoxic state.

Levy's Technique for the Anoxemia Test.—The technique of carrying out the anoxemia test* most frequently used in the United States is that of Levy and associates[53] (p. 634) and is described by him as follows:

"A tank containing a mixture of 10 per cent oxygen and 90 per cent nitrogen furnished an unvarying concentration of oxygen in the inspired air. The oxygen mixture was admitted at a rate comparable to that of normal pulmonary ventilation. The gas was allowed to flow through a humidifier, into a rubber bag, which was kept full but not distended. Two flutter valves were incorporated in such a way that the mixture was inhaled during inspiration and exhaled during expiration without rebreathing. A two-way valve at the mouthpiece enabled the observer to connect the patient to the apparatus while he was breathing room air, and thus accurately to record the time at which the subject began breathing the low-oxygen mixture. A tank containing 100 per cent oxygen was also in the circuit, so that, if desired, by turning a needle valve, anoxemia could be relieved quickly.

"Observations were made at least two hours after the last meal. The temperature in the room at which the test was made was kept reasonably constant at about 72° F. The subject was allowed to rest quietly in bed from a period of thirty minutes to one hour. The procedure was explained and he was told that if he experienced pain in the chest or arms he should at once raise his hand. The electrodes were applied and remained in place throughout the test. The mouthpiece of the gas apparatus was then inserted and the nose clamp adjusted. The subject was allowed to breathe room air through the valve of the apparatus for a few minutes. At this time

*A satisfactory apparatus for carrying out this test has been made by Forreger and Co., New York, N. Y.

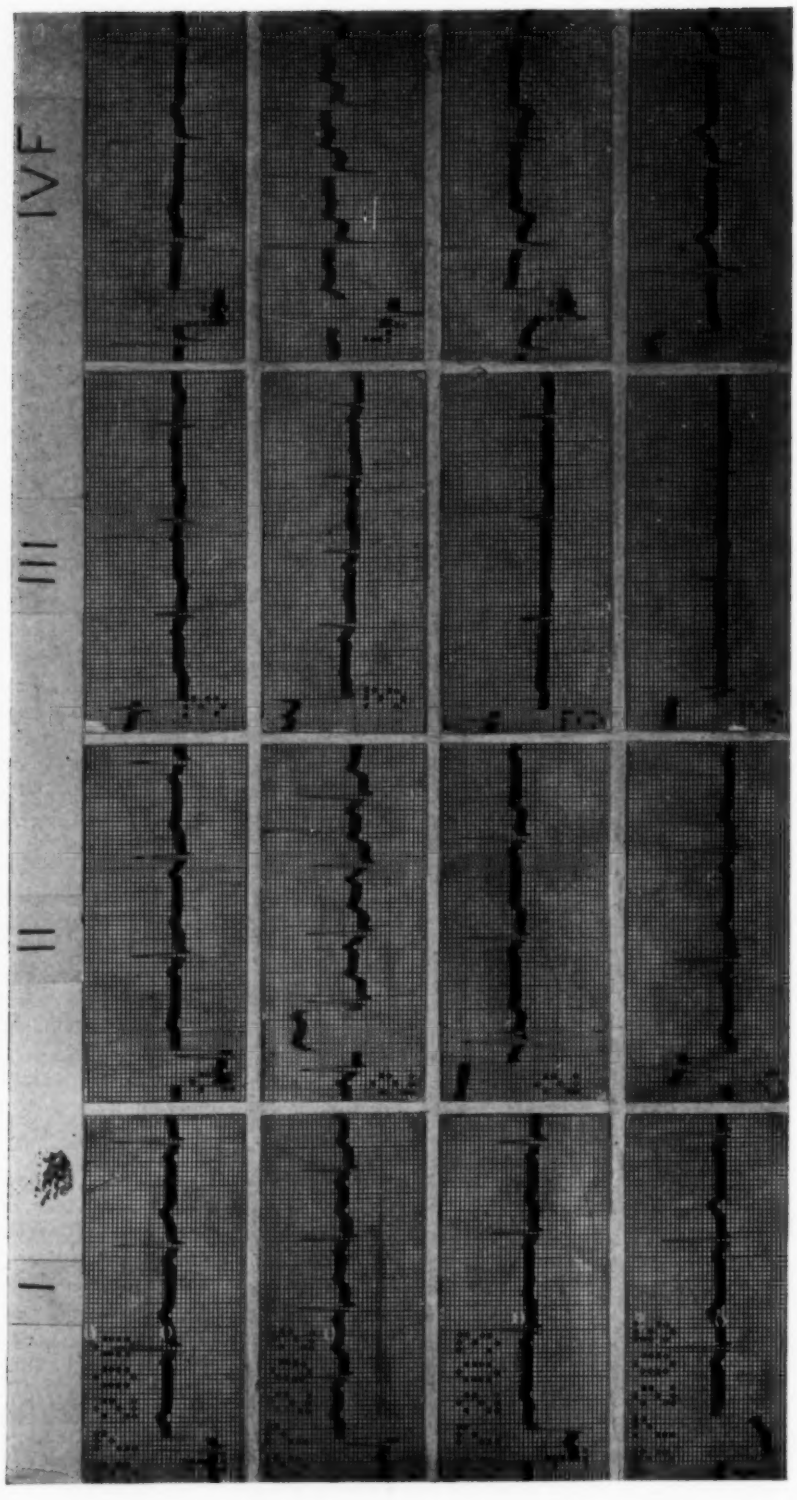

Fig. 1.—The pertinent electrocardiograms of patient B. C. in whom the anoxemia test was positive (see text). The standardization was such that 1.0 cm. deflection of the string represented 1.0 millivolt. *A*, Control. *B*, 10 per cent O_2 to 90 per cent N_2 for 10 min. after pain. *C*, Taken 1 min. after 100 per cent O_2. *D*, Record made 10 min. after 100 per cent O_2.

a four-lead electrocardiogram was taken as a control.* The precordial lead was the one commonly designated IV F. The test was then started by closing the valve, the subject was unaware of this maneuver."

Electrocardiograms are then taken at five-minute intervals through a twenty-minute period, unless substernal or precordial pain or discomfort occurred earlier. At the completion of the test the patient inhaled 100 per cent oxygen for a period of one minute, or until pain had disappeared. Electrocardiograms were also taken at intervals of one, five, and ten minutes after starting to breathe 100 per cent oxygen. In each lead measurements of the deviation of the RS-T junction were taken as the difference between the point just preceding the initial deflection of the QRS and the point immediately following the final deflection. The measured complexes should run horizontally, the deflection of the string should be accurately standardized, and the skin resistance kept low.

It is recommended that the technique which has been described by Levy be followed in the clinical use of the anoxemia test.

In Fig. 1 is shown the electrocardiograms derived from a patient in whom the anoxemia test was positive. B. C., a man, 58 years of age, had had attacks of substernal pain for six years. The pain was squeezing in character and without radiation. The pain usually came on with exertion such as walking one to two blocks and was relieved immediately by nitroglycerine.

During the anoxemia test the patient experienced pain similar to the spontaneous pain suffered on exertion and electrocardiographic changes sufficient to indicate a positive test developed (Fig. 1).

PRECAUTIONS TO BE FOLLOWED IN CARRYING OUT THE ANOXEMIA TEST

In the performance of an anoxemia test by whatever method is used, it is essential that the control record be examined before the test is started in order to avoid carrying out the test in patients with electrocardiograms which obviously indicate coronary artery disease and in patients who have suffered recent myocardial infarctions. With respect to this precaution, Turner and Morton[104] have especially advised that the control electrocardiogram consist of the twelve leads because ". . . on a number of occasions when four leads were normal we found evidence of infarction on taking further leads." The test should not be done if myocardial infarction has occurred within four months, if there is evidence of congestive heart failure, of if a previous anoxemia test has been done within the preceding 24 hours. Stewart and his associates[99] list the following additional contraindications to employment of the test: congenital heart disease, rheumatic heart disease with valvular damage, pregnancy, myxedema, epilepsy, marked emphysema, or other pulmonary disease, and severe anemia.

UNTOWARD REACTIONS, ACCIDENTS, AND DEATHS DURING ANOXEMIA TESTS

On the whole, serious untoward reactions have been few. Mild fullness of the head, dryness of the mouth, lightheadedness, sense of lack of air, and moderate

*This control electrocardiogram is always checked before the test is begun.

headache may occur during the test. These symptoms are usually relieved by breathing 100 per cent oxygen and are not serious enough to prevent the test being used. It has been the common experience that many nervous and unstable individuals may be unable to cooperate satisfactorily in breathing through the apparatus used in anoxemia tests and may require more than one attempt before a satisfactory performance is achieved. In working with patients in this group this experience is not uncommon when they are required to participate in laboratory procedures.

Vasovagal attacks are the most common untoward reactions which are encountered. The following signs and symptoms in varying combinations characterize the vasovagal episodes: weakness, sweating, pallor, marked slowing of the heart rate, fall in arterial blood pressure, lightheadedness, syncope and occasionally nausea. Other symptoms which may occur are drowsiness, fatigue, choking sensation, heavy sensation in the chest, tingling and numbness of the fingers, hyperventilation, and fear and anxiety.

In the report of Levy and associates[52] made in 1941, the test had been carried out 1,024 times in 442 patients. Unpleasant reactions were encountered forty-six times in thirty-six patients. Vasovagal attacks were observed eight times in six patients. In the large series of 1,130 tests reported by Nylin and associates[70] one vasovagal attack was recorded. Apparently, this reaction need not be expected in more than 5 per cent of tests.[9]

Disturbances of cardiac rhythm and conduction have been recorded occasionally (Levy and associates,[53] Böirck,[11] and Stewart and associates[99]). Pruitt and associates[79] observed a brief period of cardiac standstill. These abnormalities apparently reflect the reactions of the individual to anoxia with increased vagal tone.

Mild convulsive seizures, loss of consciousness, panic, dyspnea, and hyperventilation have been reported. In Levy's experience[45] acute pulmonary edema occurred on three occasions, promptly subsiding with the administration of oxygen, morphine, and rest. Stewart and his associates[99] have reported the occurrence of a petit mal seizure in a known epileptic. Transient mental confusion has been reported in elderly patients.

In all the reports which are available there have been but two fatalities. Both of these were reported by Levy.[45] They occurred because of failure to detect the presence of recent myocardial infarction by neglecting to examine the control records of the patients immediately before the tests were begun. In one patient the diagnosis was confirmed by autopsy. In the second patient, autopsy was not done. In this patient, however, ventricular paroxysmal tachycardia appeared and persisted after seven minutes of anoxemia, and the patient died four hours later. The control record, when examined later, indicated that myocardial infarction had occurred recently.

TECHNIQUES OTHER THAN LEVY'S FOR THE ANOXEMIA TEST

Instead of using the apparatus and technique as described by Levy, some observers[17,24,73,74,76,106] have used a gas mixture administered and regulated by a standard anesthesia machine, such as the Heidbrink apparatus, with or without

a positive pressure ball-valve mask. It has already been mentioned that oxygen concentrations of 9, 10, and 12 per cent have been used. In an effort to attain more uniform results, carbon dioxide has been added to the oxygen-nitrogen mixture by some investigators.

Malmström[61] used 4.5 per cent carbon dioxide and 6.5 per cent oxygen in nitrogen as one mixture and 9 per cent oxygen in nitrogen as another mixture. His criteria for abnormality with his modification were as follows: (1) inversion of T_1, T_2, and T_4 or inversion of T_3 if right-axis deviation were present; (2) S-T deviation of 2.5 mm. above the isoelectric level or 1.0 mm. below the isoelectric level in any lead.

Hecht[32] used a breathing mixture consisting of 10 per cent oxygen, 87 per cent nitrogen, and 3 per cent carbon dioxide. He evaluated the electrocardiographic changes according to Levy's criteria.

A closed Plexiglass chamber has been used by Mannheimer[62] in making observations on children. Decompression chambers have for the most part been employed on aviation studies.[16,21,103] Rebreathing apparatus using a principle of gradually diminishing inspired oxygen (the CO_2 being absorbed by soda-lime) has had considerable use experimentally, but the effects of such tests are difficult to evaluate. More recently, Holbrook and Shapiro[34,35] have taken up this phase again and have been attempting to standardize the criteria for a test based on anoxia induced by rebreathing. This is still in the experimental stage. It must be kept in mind that this last method, namely, rebreathing, as a clinical procedure may be dangerous.[31,37,68,88]

None of these modifications which have been mentioned appear to have contributed significantly to the efficiency of the standard test as devised by Levy. Nevertheless, it is important to apply the method of each author as specifically indicated if results which are strictly comparable are to be obtained. It is also important to keep in mind that the criteria relating to the anoxemia test, as established by Levy, apply to barometric pressure prevailing approximately at sea level. It has been demonstrated that tests performed according to Levy's technique did not give comparable results, as should be expected, when carried out at an altitude of about 5,000 feet.[5,72]

CHANGES IN THE Q-T INTERVAL DURING THE ANOXEMIA TEST

Anoxia is recognized as one cause for prolongation of the Q-T interval in the electrocardiogram.[3,7,84-86,107] With this background Roehm and associates[87] in 1954 studied the duration of electrical systole as measured by the Q-T interval corrected for the heart rate during the Levy anoxemia test in a group of forty normal men and ninety-five male patients. The initial $Q\text{-}T_c$ durations were higher in patients with angina pectoris than in the control group. During the anoxia of the anoxemia test prolongation of the $Q\text{-}T_c$ interval occurred which was much greater in patients with angina than in normal subjects as well as in patients with chest pain which was not cardiac in origin. Because of the wide range of response the differences were not adequate to separate normal and abnormal reaction to anoxia. They found that, if the maximal increase in $Q\text{-}T_c$

interval during the anoxemia test was plotted against the control (initial) Q-T_c value for all subjects and patients, an oblique line could be drawn which separated most of the patients with angina pectoris from nearly all patients without angina. The equation for this line was: 0.480 sec. = initial (Q-T_c) + 2.6 times the maximal increase in the Q-T_c interval during anoxia. In short, the upper limit of normal for the value derived by adding to the initial Q-T_c interval 2.6 times the maximal increase in Q-T_c interval occurring during anoxia is 0.480 sec. They have designated this value the "Q-T Anoxemia Index." They found by the "Q-T Anoxemia Index" that the test was positive in 89.5 per cent of patients who were thought to have true angina pectoris, in contrast to 55.2 per cent of these tests which were positive according to Levy's criteria.

ARTERIAL OXYGEN SATURATION PREVAILING DURING ANOXEMIA TESTS

Many investigators have recorded the arterial oxygen saturation during the anoxemia test, either by direct measurement, or indirectly, by using a Millikan oximeter.[4,9,42,48,49,61,66,73,74,76] The range of saturation varied from 88 to 35 per cent at the end of 20 minutes of breathing 10 per cent oxygen.[4] The range of oxygen saturation commonly prevailing for this interval of breathing is 70 to 80 per cent. In investigating the oxygen saturation of the blood and changes in the electrocardiogram, blood pressure and heart rate during the anoxemia test Mathers and Levy[66] recently performed 109 tests on ninety-seven subjects. In forty-five patients the diagnosis was coronary sclerosis and in fourteen, the diagnosis of coronary artery disease was in doubt. Thirty-eight individuals were normal subjects. These investigators made oximeter readings during and after the test. They found, as Levy and others[48] had previously observed, that the level of anoxemia varied widely in the same and in different individuals. After breathing 10 per cent oxygen for 20 minutes the range of arterial oxygen saturation recorded by the readings of a Millikan oximeter for the various groups varied between 71 and 75 per cent, with an average for all individuals of 73 per cent.

Levy and his associates were unable to demonstrate an optimal range of oxygen saturation which caused electrocardiographic changes characteristic of a positive test. The determining factor appeared to be the degree of impairment in the functional capacity of the coronary circulation. The electrocardiographic changes occurred over wide levels of anoxia. Although the majority of the electrocardiographic changes occurred in the first ten minutes of the test, a certain number of the tests became positive in the last half of the test, especially in the last five minutes. It was, therefore, considered advisable to carry the test for the full twenty minutes unless the patient experienced pain or discomfort before the end of that time.

Penneys and Thomas[75] produced controlled anoxemia at levels of 80, 75, and 70 per cent arterial oxygen saturation in seventy-six normal young adults. The subjects compensated physiologically to these levels. None of the thirty subjects in whom the oxygen arterial saturation was reduced to 70 per cent during the test exhibited untoward effects. They found that the degree of cardiovascular response closely correlated with the level of arterial oxygen saturation

and that maximal electrocardiographic changes in these normal subjects were smaller than the minimal criteria established by Patterson and associates[72] for the anoxemia test. They suggested the possibility of an intermediate zone between the normal and abnormal which might indicate a "doubtful positive" reaction. They considered it important to know the arterial oxygen saturation in those patients with "presumptive positive" reactions, that is to say, in those patients having anginal pain but a negative electrocardiographic test. They observed also that the pattern of response varied considerably from subject to subject, althouth the type of cardiovascular response of the same subject was similar at different levels of anoxemia.

More recently, Tewell and Pritchard[102] reported a controlled hypoxemia test. Using a Heidbrink anesthesia apparatus for control of the oxygen mixture and a Millikan oximeter for estimating the arterial oxygen saturation, they adjusted the oxygen-nitrogen flow so that patients maintained a continuous level of 70 per cent arterial oxygen saturation for a period of up to twenty minutes. At the usual intervals, 12-lead electrocardiograms were taken. They considered an RS-T deviation of 1 mm. in any lead abnormal. In normal control subjects, deviation of the RS-T segment greater than 0.5 mm. did not occur, and flat or inverted T waves were not observed. In their "controlled hypoxia tests" just cited, Tewell and Pritchard[102] consider that the most important single factor affecting the sensitivity and accuracy of the test was the degree of arterial oxygen saturation. That this value is not necessarily an accurate index of the arterial oxygen tension has been indicated by Malmström.[61]

PHYSIOLOGIC OBSERVATIONS DURING THE ANOXEMIA TEST AND RECENT OBSERVATIONS

Barach and his associates[4] in 1941 expressed the opinion that the alkalosis of hyperventilation occasionally attending the anoxemia test may be a factor in impairing the coronary circulation and that the inhalation of small amounts of carbon dioxide shortened the period of recovery of cardiac muscle in part by increasing the arterial oxygen tension, and in part by preventing constriction of capillaries in the coronary circulation. Christensen[20] in 1946 observed also that T-wave and RS-T segmental changes which were induced by hyperventilation and the resulting alkalosis in normal persons could be abolished by adding carbon dioxide to the inspired air. Malmström[60] was of the opinion that the oxygen tension was a better index of induced anoxia than arterial oxygen saturation. It has been shown that, during the anoxemia test as it is commonly performed, there is a fall in the arterial oxygen saturation. The curve may be gradual or steplike, but usually a fairly abrupt initial drop occurs during the first five minutes of the test followed by a relative leveling off with maintenance of the saturation at a level of 70 to 75 per cent.[61,66,74-76] These factors may be modified by the degree of cardiopulmonary disease which the individual has and by the amount of hyperventilation which he experiences. Usually, an increase in both rate and depth of respiration is to be expected, as well as an increase in pulse rate of at least ten beats per minute. Elevation of systolic arterial blood pressure of around 10 mm. Hg may occur, although constant changes in either the heart

rate or the blood pressure cannot be predicted in certain individuals. Accompanying hyperventilation may be a diminution of the carbon dioxide content of the blood and elevation of the arterial pH.[4] The actual arterial oxygen tension varies with all of these factors.[60,109]

In studies of pulmonary vascular responses to short-term hypoxia using the catheterization technique, Doyle and associates[23] found that reduction in arterial oxygen saturation to around 75 per cent in eight normal subjects caused increases in the pulmonary vascular resistance and in cardiac output. However, in a group of twelve patients with "cardiopulmonary disease" a similar reduction of arterial oxygen saturation caused a much smaller increase in pulmonary vascular resistance and little or no increase in cardiac output. In neither group did they observe change in pulmonary capillary pressure, nor was there evidence of alteration of pulmonary blood volume during anoxia.

Biörck's[10] studies of the effects of ergonovine tartrate on the anoxemia test in unstable individuals are discussed later.

From ballistocardiographic tracings on twelve normal individuals during anoxemia tests, Scarborough and associates[91] found that there was a variable increase in cardiac output during the test.

ELECTROCARDIOGRAPHIC CHANGES OCCURRING DURING THE ANOXEMIA TEST IN PATIENTS WITH HEART DISEASE AND IN PATIENTS WITH DISEASES OTHER THAN CORONARY ARTERY DISEASE

Although the anoxemia test finds its widest clinical application in the detection of coronary insufficiency due to coronary artery disease, the electrocardiographic changes which occur are not specific for coronary artery disease, but may detect changes in the coronary circulation due to other causes. For example, patients who have coronary insufficiency of significant degrees associated with aortic valvular disease may have positive anoxemia tests.[49,52,53] Positive tests may occur in the presence of marked anemia[49] as well as in the presence of active rheumatic carditis, patent ductus arteriousus, and of unidentified types of congenital heart disease in children with and without cyanosis.[62,70] Positive tests have been observed in hypertensive subjects with large hearts.[49,52,53] Although the hypertensive individuals with cardiac enlargement probably had relative coronary insufficiency, the presence of coronary atherosclerosis in most reported cases is probable but unproved.[66]

Interesting but confusing data concern the observations that some individuals who were thought to have "vegetative lability," "neurovegetative imbalance" and neurocirculatory asthenia have been found to have positive anoxemia tests.[10,70,77] This problem has been given most attention by Scandinavian investigators. In a group of 354 patients, none of whom were thought to have cardiac diseases, Nylin and his associates[70] found that nineteen patients had positive tests. The diagnoses in them were as follows: rheumatoid arthritis, six (two with marked hyperthyroidism); neurovegetative imbalance, seven (including menopausal syndrome in three); slight hyperthyroidism, three; depressive psychosis, three. The authors stated that electrocardiograms with

abnormalities in the RS-T segments and T waves, as well as with abnormal ventricular gradients, have frequently been observed in such patients. They were of the opinion that a positive anoxemia test does not invariably indicate organic coronary artery disease but may be an expression of functional coronary insufficiency. They state: "The possibility that some neurogenic or hormonal influence may modify the electrical properties of the myocardial cells and contribute to the occurrence of a false positive result cannot be excluded."

Biörck and Pannier[14] in 1947 recorded seventeen positive tests in a group of patients who were not suspected of having coronary artery disease. Sixteen of these patients were women. Most of these patients had hypertension without cardiac enlargement and were designated by Biörck as "neuropathic." Biörck stated: "There is probably a great difference between the 'psychical' type of coronary neurosis which does not give a positive test and the 'autonomic nervous type' which occasionally does give positive tests and which ought to be treated like real disease."

There are as yet no autopsy reports on these patients. On the basis of the objective evidence they appeared to have coronary insufficiency. In another publication in 1947, Biörck[10] reported ten patients with positive tests in whom functional factors might have been responsible. In these patients a second test was done after giving ergotamine tartrate 0.5 mg., intravenously. In nine of these individuals, the second test was negative. These results indicate an effect of the sympathetic nervous system on the induction of positive tests in these patients. It is disturbing that the terms " ? myocarditis and " ? myocardial damage" appear in the list of clinical diagnoses relating to three of these patients. It is also of interest that a 29-year-old patient in whom the diagnoses were hypercholesterolemia and questionable coronary disease had a positive test both before and after ergotamine. It is well known that marked atherosclerotic changes in the coronary arteries may occur in this syndrome. Stroder[101] was unable to differentiate satisfactorily patients with supposed coronary artery disease and those with presumable vegetative imbalance (dystonic) by the use of the hypoxia test in conjunction with hydrated ergot alkaloid. He concluded that the history and clinical findings were the essential factors in such differentiation. It is difficult to interpret these findings as similar ones have not been encountered in the many carefully controlled American series.

In a series of 200 control patients, Weintraub and Bishop[106] encountered but two positive tests without pain in patients with no apparent, significant ". . . cardiovascular, hemic or emotional factors." They considered these to be either false-positive tests or examples of coronary insufficiency of obscure etiology. Mathers and Levy[66] have not encountered any false-positive reactions.

It might be mentioned that Pordy and associates[77] in 1949 reported that positive exercise tests were recorded in certain individuals with neurotic complaints. Certain of these tests which had been positive beforehand became negative when exercise was carried out after ergotamine tartrate had been given intravenously.

THE RELATION BETWEEN ELECTROCARDIOGRAPHIC CHANGES DURING THE ANOXEMIA TEST AND ANGINAL PAIN

Although it has been demonstrated that the abnormal electrocardiographic changes which occur in a positive anoxemia test are like those seen during spontaneous attacks of angina,[83,92] there is no constant correlation of these changes with the occurrence of pain. Accordingly, a positive test occurs commonly without pain. The exact frequency of this occurrence, namely, a positive test without

TABLE I. PER CENT OF POSITIVE ANOXEMIA TESTS ELECTROCARDIOGRAPHICALLY FOUND IN PATIENTS WITH TYPICAL ANGINA

AUTHOR	YEAR	METHOD	NO. OF PATIENTS	PER CENT POSITIVE TESTS ELECTROCARDIOGRAPHICALLY
Levy, Williams, Bruenn, & Carr[83]	1941	10% 0_2 (Levy)	73	55.0
Evans and Bourne[26]	1941	10% 0_2 for 3-5 min.	20	33.3
Patterson, Clark, & Levy[72]	1942	10% 0_2 (Levy)	157	49.0
Pruitt, Burchell, & Barnes[79]	1945	10% 0_2 using positive pressure mask	92	52.2
Biörck[11]	1946	10% 0_2 (Levy)	46	30.4
Biörck[9]	1946	10% 0_2 (Levy)	20	40.0
Malmström [61]	1947	4.5% CO_2 6.5% 0_2 in N_2	13	61.0
Lindgren[55,56]	1947	10% 0_2 (Levy)	87	52.0
Weintraub & Bishop[106]	1947	10% 0_2 given by anesthesia machine	20	55.0
Soupanki[98]	1948	9% 0_2 for 8 min.	32	50.0
Soupanki[98]	1948	10% 0_2 for 20 min.	32	56.0
Sjostrand and Wahlund[95]	1946	9% 0_2 for 8 min.	39	48.0
Sjostrand and Wahlund[95]	1946	10% 0_2 for 20 min.	39	48.0
Stewart, Horger, & Sorensen[99]	1948	10% 0_2 (Levy)	40	45.0
Burchell, Pruitt, & Barnes[17]	1948	10% 0_2 using positive pressure mask	730 tests*	50.0
Nylin, DeFazio, & Marsico[70]	1950	9% 0_2 for 10 min.	163	30.8
Alexander, Wittenberg, Brown, & Koffler[2]	1950	10% 0_2	34	33.0
Mathers & Levy[66]	1950	10% 0_2 (Levy)	45	47.0
Turner & Morton[101]	1952	10% 0_2 for 10 min.	30	46.6

*Number of patients not given.

pain, is difficult to determine because of the many confusing subdivisions given to the analyses in some of the published reports. This occurred in 30 per cent of Hecht's[32] group of 200 tests. In 289 tests in Pruitt's series[79] it occurred in 14.1 per cent in a group of ninety-two patients who had a history highly suggestive of angina pectoris, and in 5.6 per cent in a group of 108 patients in whom there were certain features in the histories suggestive of coronary insufficiency, as well as certain clinical manifestations of a doubtful or contradictory nature. The occasional occurrence of pain without significant electrocardiographic changes has been generally observed.[17,52,79] Levy and associates[52] reported that of fourteen patients showing negative electrocardiographic reactions but experiencing pain, 28.6 per cent later showed positive tests, and that 21.4 per cent had complications or died of heart disease. Although Biörck and Dalhamn[13] were unable to prove statistically a prognostic value in negative tests with pain, Biörck and associates[9,11,14] and also Stewart and co-workers[99] consider that such results may be regarded under certain circumstances as presumptive evidence of coronary artery disease. Stewart and his associates agree with Levy and his co-workers that the occurrence of pain should not be given weight when payment of insurance is involved. Further prognostic implications will be discussed.

TABLE II. PER CENT OF POSITIVE ANOXEMIA TESTS ELECTROCARDIOGRAPHICALLY FOUND IN PATIENTS WITH QUALIFIED ANGINA

AUTHOR	YEAR	METHOD	NO. OF PATIENTS	AUTHOR'S QUALIFICATION OF THE DIAGNOSIS OF ANGINA PECTORIS	PER CENT POSITIVE TESTS ELECTROCARDIOGRAPHICALLY
Larsen[62]	1938	9% O_2 in nitrogen	26	Moderately suspected	15.0
Levy, et al.[53]	1941	10% O_2 in nitrogen (20 min. max.)	33	"Suspected"	18.0
Pruitt, et al.[79]	1945	10% O_2 in nitrogen	108	Moderately suspected	19.5
Biörck[11]	1946	10% O_2 in nitrogen (Levy)	131	Suspected	19.8
Stewart, et al.[99]	1948	10% O_2 in nitrogen (Levy)	46	"Atypical"	18.0
Nylin, et al.[70]	1950	9% O_2 in nitrogen (10 min. max.)	73	"Probable"	16.4

THE VALUE OF THE ANOXEMIA TEST FOR THE DIAGNOSIS OF CORONARY ARTERY DISEASE

Approximately 25 per cent of patients with coronary artery disease who suffer from attacks of angina pectoris have no objective evidence of heart disease.[108] In these patients the occurrence of symptoms typical of angina together

with the history of relief of the distress by the administration of nitroglycerine sublingually is adequate evidence to make the diagnosis of angina pectoris due to coronary artery disease. There is, however, a group of patients in whom the diagnosis cannot be made so easily. In 15 to 20 per cent of the patients in this group the anoxemia test might be expected to be positive (Table II). It is strongly emphasized again that negative tests do not exclude the presence of coronary artery disease.

The experiences with the clinical use of the anoxemia test reported during the past fifteen years both here and abroad have been fairly uniform. They will be briefly reviewed. Certain data from them are found in Tables I and II.

In 1941 Levy and his associates[53] re-evaluated and extended the work which had been published in 1939 and proposed the four criteria, which have been mentioned for the detection of positive tests. Positive tests were present in 18 per cent of thirty-three patients with histories which indicated that they probably had anginal pain, but in whom there were no abnormal physical signs and in whom the electrocardiograms were normal. The test was positive in 31 per cent of twenty-two patients who had no history of anginal pain, but exhibited either abnormal electrocardiograms or enlarged hearts; and it was positive in 55 per cent of seventy-three patients who had abnormal electrocardiograms or enlarged hearts plus a history of anginal pain. A positive test was not encountered in 115 normal subjects. Later in 1941 Levy and his co-workers[52] reported data relating to 373 tests carried out in 137 patients. They emphasized that a negative test did not exclude the diagnosis of coronary artery disease. They suggested, as mentioned above, that a negative electrocardiographic test when coupled with the occurrence of pain might be considered as presumptive evidence of coronary sclerosis. Patterson and co-workers[72] in 1942 found positive anoxemia tests in 49 per cent of 157 patients with coronary sclerosis, and another 20 per cent of the patients in this group had negative electrocardiographic tests although they experienced pain. They considered that the occurrence of pain during the first ten minutes of a negative electrocardiographic test was of particular importance. Because the fourth criterion (namely, partial reversal of the direction of the T waves in Lead IV F accompanied by an RS-T deviation of 1 mm. or more in this lead) was the sole criterion of a positive test in less than 2 per cent of the cases of coronary sclerosis and had the same incidence in normal subjects, the use of this sign was discontinued.

Early in 1942, Burnett and associates[5] working in Denver carried out the anoxemia test in 125 individuals who were thought to be normal. They found abnormal responses in 19.2 per cent of these according to Levy's third criterion. These abnormalities were distributed fairly evenly in the age groups from twenty-one to sixty years. They found untoward symptoms seventeen times in 189 tests. On the basis of their experience they considered the test dangerous and unreliable. A similar experience was not shared, however, by Deeds also of Denver (discussion).[5] With respect to the results obtained by Burnett and his associates, Patterson and associates[72] later in 1942 made two criticisms: in the first place they raised the question whether the hearts were normal in all of their subjects.

In the second place, they were of the opinion that the results of the tests carried out by Barnett and his associates in Denver at an altitude of approximately one mile above sea level were not comparable to those obtained at sea level. It appears, therefore, that the results secured by Burnett and his associates cannot be compared with the results of the anoxemia test as described by Levy. This opinion has been generally accepted.

The experience of other American workers with the anoxemia test has been on the whole similar to Levy's. Pruitt and associates[79] in 1945 and Burchell and co-workers[17] in 1948 reported observations in 289 patients. Positive tests were obtained in 53 per cent of ninety-two patients with typical angina; and positive tests were secured in 19 per cent of 108 patients with questionable angina. They reported later in 1948 that a total of 730 tests had been carried out in their clinic. They concluded that positive anoxemia tests were to be expected in 50 per cent of patients when coronary artery disease of clinical magnitude was present. They were of the opinion that breathing the low-oxygen mixture for fifteen minutes induced as many positive tests as when it was breathed for twenty minutes as recommended by Levy. They had no fatalities in their large series.

Weintraub and Bishop[106] in 1947 reported the results in 220 patients. Twenty of these patients had clinical evidence of coronary insufficiency; eleven of these, that is to say, 55 per cent, had positive tests.

Stewart and co-workers[99] in 1948 using Levy's technique performed 138 tests on 119 subjects. In this group twenty-six normal subjects were used as controls and in all of them the tests were negative. The test was positive in 45 per cent of forty patients with typical angina. The test was positive in 13 per cent of forty-six patients with atypical angina. They had no occasion to observe that negative tests with pain later became positive. They observed that 63 per cent of the typical angina group developed pain in contrast to 27 per cent of the atypical group; moreover, 38 per cent of the typical group had pain in the first ten minutes in contrast to 17 per cent of the atypical group. They found that although hypertension had no apparent effect statistically in increasing the incidence of coronary insufficiency in the group with typical pain, it did so in the group with atypical pain. Cardiac enlargement in the atypical group increased the likelihood of a cardiac origin of the discomfort. The presence of both cardiac enlargement and hypertension in the atypical group increased the incidence of positive tests. In the typical group, neither cardiac enlargement nor hypertension had any apparent effect in statistically increasing the incidence of coronary insufficiency.

Hecht[32] in 1949 reported the results of 200 tests in 113 patients. He used a mixture of 10 per cent oxygen, 87 per cent nitrogen, and 3 per cent carbon dioxide. When breathing this mixture for a maximal period of twenty minutes, twenty-one normal subjects had negative tests. In ninety-four tests performed on fifty anginal patients, 44 per cent were positive with pain and 31 per cent were positive without pain. Sixty-eight tests were performed in forty-seven patients having histories of previous myocardial infarctions. In these, 28 per cent were positive with pain, and 38 per cent were positive without pain.

Alexander and co-workers[2] performed forty-two tests on thirty-four subjects with angina. Seventeen had pain during the test, and eleven of these had significant electrocardiographic changes.

Mannheimer[62] in 1946 made observations in eighty-four children using 10 per cent oxygen for a period of ten minutes. The children were enclosed in a Plexiglass chamber. In thirty normal children all tests were negative for this time interval of breathing. In sixteen of twenty-five patients suffering from various cardiac abnormalities the tests were positive. In nine of twenty-nine patients in whom third heart sounds were heard positive tests were recorded, an observation giving support to Calgren's theory[18] that a third sound gallop indicates myocardial injury.

Wide interest has been displayed in the anoxemia test in the Scandinavian countries. Although both the methods of induction of anoxemia and the oxygen content of the gas mixtures have been varied, all of the electrocardiographic results have been evaluated according to Levy's criteria. There is overlapping of material presented in the individual reports, and they will be discussed together under the name of the principal author in each case.

Nylin[69] in 1943 in an initial series made up of 163 patients in whom he used Levy's technique of the anoxemia test found an over-all incidence of 22 per cent positive tests. In those patients who had anginal pain but who were without other evidence of heart disease, the incidence of positive tests was 63 per cent. Subsequently, Nylin and associates[70] in 1950 presented an analysis of 1,130 tests performed in 1,103 patients. In this latter series, a mixture of 9 per cent oxygen in nitrogen was breathed for a maximal period of ten minutes. The incidence of positive tests in 136 anginal patients was 30.8 per cent; in seventy-three patients with probable angina positive tests occurred in 16.4 per cent; and in 131 cases of doubtful angina, the incidence of positive tests was 9.9 per cent. In the whole series the test was positive according to Levy's second criterion alone in only two cases; in all others the sum of the RS-T deviations was greater than 3 mm. In only three of thirty-four instances of anginal pain did negative tests occur.

Malmström[61] in 1947 presented an excellent review of the subject. In his observations he used two breathing mixtures. One of these mixtures was 9 per cent oxygen in nitrogen. The other was composed of 4.5 per cent carbon dioxide and 6.5 per cent oxygen in nitrogen. The end result from breathing this last mixture was that the variations in oxygen tension and saturation at the end of the test were relatively small as compared to those in tests carried out without the addition of carbon dioxide in which the mixture was composed of 9 per cent oxygen in nitrogen. Using Levy's criteria, tests were negative in forty-three normal subjects 19 to 30 years of age, and in eleven subjects over forty years of age with suspected "myocardial injuries." Eight of thirteen patients with angina, that is to say, 61 per cent, gave positive tests. Accordingly, the breathing of mixtures low in oxygen with the induction of low-arterial-oxygen saturations did not appear to have appreciably increased the frequency of the occurrence of positive tests and therefore did not raise the efficiency of the test as compared with other series which were performed in the usual way.[48,49]

Lindgren[56-58] in 1946 to 1947 carried out anoxemia tests in two series of anginal patients using Levy's technique. In the first series of forty-nine anginal patients, positive tests occurred in forty-five patients; thirty-four of these patients had abnormal resting electrocardiograms. Fourteen of fifteen anginal patients with normal resting electrocardiograms had positive tests. In a subsequent experience with eighty-seven patients there were forty-five positive tests, that is to say, an incidence of 52 per cent, results which are within the usual range for other large series of cases.

Sjostrand and Wahlund[95] in 1946 studied thirty-nine patients with coronary artery disease who had angina of effort. They used 9 per cent oxygen for a period of eight minutes and 10 per cent oxygen for twenty minutes. There was no significant difference in the incidence of positive tests with the two different mixtures, since it was 48 per cent in each.

Biörck's[9,11,12] many observations prior to 1947 have been well summarized in the AMERICAN HEART JOURNAL of that year. These data concerned a total of 350 anoxemia tests done on 326 patients using a mixture of 10 per cent oxygen and 90 per cent nitrogen. If patients with evidence of other cardiac disease, of respiratory impairment, and of severe anemia were excluded he found that there were no positive tests in the group of normal subjects or of those "slightly suspected" of having angina. Positive tests occurred in 20 per cent of patients with "moderately suspected" angina. In patients with "probable or certain" coronary artery disease, 30 to 50 per cent gave positive tests. In a further publication in 1947, Biörck and Pannier[14] analyzed 100 positive tests occurring in observations of 666 patients. Forty positive tests occurred in 378 men, and sixty positive tests were encountered in 288 women.

Soupanki[96] in 1948 observed 100 patients using two tests: in one test he used 9 per cent oxygen for 8 minutes and in the other tests 10 per cent oxygen for 20 minutes. The incidence of positive tests was essentially the same in both, namely, thirty-four with 9 per cent oxygen, and thirty-five with 10 per cent oxygen. There were thirty-two patients with angina. In them, positive tests occurred in sixteen, namely, 50 per cent, with 9 per cent oxygen, and in eighteen, namely, 56 per cent, with 10 per cent oxygen. There were forty-two patients with "atypical angina." Positive tests occurred in four, namely, 9.5 per cent when 9 per cent oxygen was used, and in three, namely, 7 per cent, when 10 per cent oxygen was used. In short, the use of the lower oxygen percentage did not significantly change the incidence of positive tests.

In England, Evans and Bourne[26] in 1941 reported the results in twenty patients with angina who breathed 10 per cent oxygen from a bag for three to five minutes. In six of these, abnormal electrocardiographic changes were recorded.

In 1952, Turner and Morton[104] reported observations in fifty-one individuals. Twenty-one subjects served as controls. One control, a 40-year-old man without symptoms, had a positive test according to Levy's third criterion, namely, the RS-T deviation in Lead IV was 3 mm. In a group of thirty patients, fourteen had positive tests and sixteen negative ones, according to the objective electrocardiographic criteria. Eleven patients experienced pain during the test, nine

of whom had positive electrocardiographic tests and two negative ones. Turner and Morton employed 10 per cent oxygen breathed for ten minutes only. They selected this time interval because they found it "quite sufficient" and, moreover, they found that electrocardiographic changes might ". . . actually regress after this time owing presumably to compensatory effects." This phenomenon has been observed also by other investigators.

In 1950 in the United States, Mathers and Levy[66] recorded observations in an additional group of forty-five patients with coronary sclerosis. Fifteen of these patients completed the test with negative electrocardiographic effects, nine others having uncompleted tests with negative electrocardiographic effects. Eight patients who completed the tests had positive electrocardiographic changes and thirteen patients in whom the test was interrupted gave positive electrocardiographic alterations.

The findings of the reports which have been given in detail are summarized in Tables I and II. There were variations in the technique of carrying out the test in the different reports relating to the percentage of oxygen breathed and the length of time the gas mixture was breathed, in the number of patients studied by each observer, and in the selection and diagnostic classification of patients. Taking into account these variables, it is not surprising that the incidence of positive tests in clinical coronary sclerosis ranged from a low of 30 to a high of 61 per cent in the series shown in Table I. It appears, however, that the general incidence of positive tests carried out according to Levy's technique and the results evaluated according to Levy's criteria, in this wide and varied collection of anginal patients, is approximately 50 per cent.

THE VALUE OF THE ANOXEMIA TEST AS A GUIDE TO PROGNOSIS IN CORONARY ARTERY DISEASE

It has already been stated that patients having negative electrocardiographic tests with the occurrence of pain may later develop positive tests and may subsequently die of heart disease. It has been strongly emphasized by all workers that negative tests do not exclude the presence of coronary artery disease. Burchell and his associates[17] in follow-up studies of 200 cases over a period of three to six years found that those patients with coronary artery disease having positive tests had as good prognoses as those with negative ones. It has been observed by Levy and his associates and also by Biörck that patients with positive tests may subsequently have negative ones. Biörck and Dalhamn[13] in 1950 attempted to evaluate the prognostic value of the test. They obtained follow-up information on 243 patients in whom anoxemia tests were done between the years 1942 and 1946. They found that the average life expectancy was much lower for the men in this group than for the women, and that in men the mortality rate from cardiac disease was greater in those having positive than in those with negative tests. From analysis of their data they arrived at the opinion that it was not possible to decide whether a "doubtful" test had any significance. They recorded five cardiac deaths which occurred less than six months after negative tests. With respect to the hypertensive group of patients they were of the opinion that clinical judgment was a better guide to prognosis than the anoxemia test.

Mathers and Levy[67] in 1952 presented follow-up data on 254 patients who participated in Levy's studies during the period from 1937 to 1947. Of these 103 had no evidence of cardiovascular disease and had negative anoxemia tests. At the end of six years the mortality rate of this group was 10 per cent. The following observations were made about a group of 100 patients with clinical coronary disease at the end of the six-year period. In those who had had a positive test by electrocardiogram and who had pain at the time of the test, the mortality rate was 45 per cent. In those who had a negative test by electrocardiogram but who had experienced pain at the time of the test, the mortality rate was 36 per cent. In those who had a negative test by electrocardiogram and no pain at the time of the test, the mortality rate was 21 per cent. At the end of eight years, in those who had coronary sclerosis clinically and a positive test, the mortality rate was 61 per cent; while those with coronary sclerosis but a previously negative test had a mortality rate at the end of eight years of 28 per cent.* Over the nine-year follow-up period sixty-three patients are known to have died, and sixteen autopsies were performed. In all patients who were in the clinical group of coronary sclerosis, the diagnosis of coronary artery atherosclerosis was confirmed. How many of these patients had previous negative or positive anoxemia tests is not stated.

Analyzing their data statistically, conclusive correlations could not be found between the results of the anoxemia test, the clinical status of the patient, and prognosis. In comparing curves of mortality rates, those patients with coronary artery disease and positive anoxemia tests as a group had worse prognoses with respect to longevity than did those with negative tests. It was emphasized, however, that this prognostic import could not be applied to individual patients. Mathers and Levy[67] stated that: "The anoxemia test furnishes an index of the coronary reserve only at the time of its performance. Because of the numerous uncontrollable variables affecting the lesions of atherosclerosis, it is not possible to predict accurately, within a wide range of probability, the future clinical course of the patient with coronary heart disease."

AUTOPSY REPORTS IN PATIENTS WHO HAVE HAD ANOXEMIA TESTS

Up to the present time there have been few autopsy reports on patients who have had either positive or negative anoxemia tests. In a follow-up study of 254 subjects Mathers and Levy[67] state that sixty-three patients are known to have died and in this group sixteen autopsies were performed. The clinical diagnosis was confirmed in every case. In the group with the diagnosis of coronary sclerosis with anginal pain, forty-three patients had died and in ten of these autopsies were performed, all confirming the diagnosis of coronary artery disease. In these groups it is not stated how many previously had positive or negative anoxemia tests. In addition to the patient mentioned earlier who died as a result of the anoxemia test being performed in the presence of a recent myocardial infarct, Levy has detailed four other autopsies. There was one patient who had had a negative anoxemia test twenty-four months before he died of gastric carcinoma.

*The actual numbers in each of these groups are not stated.

The heart at autopsy was unremarkable. Another autopsy was performed in a man who had had an old posterior basal infarct three and one-half years before death; he had a negative anoxemia test eight months before his death from peritonitis. The heart showed, as was to be expected, the healed scar of the earlier myocardial infarct and advanced coronary artery sclerosis. In a third patient a negative anoxemia test with pain after six minutes had been recorded 19 months prior to death; moreover, additional negative tests were recorded 18, 15, and 2 months before death. This male patient, 39 years of age, had angina, prolonged auriculoventricular conduction, a slightly enlarged heart, and a systolic murmur at the apex. At autopsy an advanced degree of coronary artery sclerosis and a recent myocardial infarct were found. A fourth patient had mild hypertension, slight cardiac enlargement, and an abnormal electrocardiogram showing right bundle branch block and prolonged auriculoventricular conduction. An anoxemia test was positive two and one-half months before death from postoperative pneumonia. At autopsy coronary artery sclerosis was present with widespread fibrosis of the posterior wall of the left ventricle.

Biörck and Dalhamn,[13] in a follow-up study of 343 patients on whom anoxemia tests had been performed from 1942 to 1946, reported that sixty-six patients had died later, and in them eighteen autopsies were performed. It is not stated how many of these had positive or negative anoxemia tests. The exact autopsy findings of those dying of heart disease were not clearly stated. In an earlier report, however, Biörck[11] has referred specifically to five autopsies, the reports of which will be mentioned.

One patient who had had a positive anoxemia test was found to have considerable coronary artery sclerosis and recent coronary thrombosis. A patient in whom the anoxemia test was doubtful was found at autopsy to have dilatation of the right side of the heart without evidence of coronary sclerosis. A third patient having a negative test had " . . . extremely narrowed coronary vessels." A fourth patient with a negative test who showed a ". . . cardiosclerotic curve at rest" had cardiac hypertrophy and dilatation and moderate coronary sclerosis. And finally, another patient in whom the anoxemia test was normal had typical mitral stenosis without coronary artery disease.

In summary, therefore, as meager as these reports are, they bear out the observation that a negative anoxemia test does not exclude coronary artery disease. There have been no reported instances of patients who have had a positive anoxemia test who have at autopsy been free of significant heart disease.

METHODS, OTHER THAN THE ANOXEMIA TEST, FOR DETECTION OF CORONARY INSUFFICIENCY

Other methods have been employed for detecting evidence of coronary insufficiency, but in most instances comparison of these results with those obtained on the same patients during the anoxemia test are not available. Katz and associates,[38] Levine and co-workers[44] and others have employed epinephrine, and Stein and Weinstein[97,98] have used ergonovine maleate for the induction of anginal pain and electrocardiographic changes. A "meal test" has been de-

scribed by Simonson and McKinlay.[94] Holbrook and Shapiro[34,35] have been investigating the standardization and evaluation of criteria for a test based on anoxemia induced by rebreathing air.

The other test in widest use in appraisal of the efficiency of the coronary circulation is the "two-step" exercise tolerance test described by Master. Its method of performance and the criteria of abnormality as reflected in the literature are variable.[90] Master and co-workers[63,65] have a described standardized procedure for its performance and have defined criteria for evaluation of the data. The results obtained in the exercise test in the direction of providing evidence of coronary insufficiency are not invariably comparable to those secured in the anoxemia test; either test may occasionally be positive when the other is negative or doubtful. The correlation between the two tests is closer in patients with typical angina than in those with atypical pain.[99] Biörck[9,11] is of the opinion that the two tests are equally safe and that much of the usefulness of the exercise test depends on the criteria which are used. There was no appreciable difference in the results of the two tests in his small comparative group; nevertheless, one test may be positive when the other is negative, or vice versa. Stewart and his associates[99] found in a small group that 70 per cent of those with typical angina had positive exercise tests as compared with 45 per cent with electrocardiographic positive anoxemia tests, or compared with 65 per cent when pain occurring in the first ten minutes of the anoxemia test was included as one of the criteria. The anoxemia test was positive once when the exercise test was negative. Storch and Master[100] made comparative studies of the two tests in twenty-three patients. They found that twelve patients gave negative results in both tests; five yielded positive tests in both; six patients gave positive results in the exercise test but negative ones in the anoxemia test. All of the patients were thought to have heart disease. These authors commented that there were many differences in the two tests and that they could not be used interchangeably. A review of the status of the exercise test has been presented recently by Scherf and Schaffer.[90]

A combination of exercise and breathing 10 per cent oxygen in nitrogen has been studied by Akesson and Malmström[1] in a group of twenty-five normal individuals and in a series of fifteen patients with angina. Abnormal changes were not encountered in the normal control group. On the other hand, all the angina patients had positive tests. This work has not been repeated by other investigators.

USE OF THE ANOXEMIA TEST IN EVALUATION OF THE EFFECTS OF DRUGS

Levy and co-workers[50] have used the anoxemia test to evaluate the effect of certain drugs: namely, nitrites, digitalis, and aminophylline, the latter both intravenously and orally. Further work by this group[110] demonstrated that nitroglycerine sublingually, and aminophylline intravenously caused prolongation in the time of appearance of pain and diminution of the amount of the RS-T changes occurring during the time of exposure to anoxia. The fact that nitroglycerine may modify the anoxemia test favorably is emphasized, as Scherf and Schaffer[90] in referring to Larsen's earlier work have recently stated that "The

administration of nitroglycerine often converts a positive exercise test into a negative one but does not influence the outcome of the anoxia test." The effects of xanthine drugs in various doses by mouth on previously positive anoxemia tests in studies by Levy and associates[50,110] were indecisive as a group, but the drugs influenced favorably the electrocardiographic changes in some individuals. These experiments were well controlled and are statistically valid. A study of effects of intravenous aminophylline on positive anoxemia tests was made by Stewart and his associates[99] with results similar to those reported by Levy.

Best and Coe[8] in 1950 used the anoxemia test in evaluating the effects of khellin in nine patients. They concluded that the drug, as compared to a placebo, was ineffective in reversing positive anoxemia tests in the doses given.

Proger and Dekamas[78] in 1946 reported observations on the effects of cytochrome C in four patients who had positive anoxemia tests. When the anoxemia test was carried out immediately following the administration of cytochrome C, 60 mg. intravenously, electrocardiographic changes did not occur. Other investigators have failed to confirm these observations.

COMMENT

From clinical experiences with the anoxemia test which has been reviewed, the following general statements may be made concerning the test and its use.

It is apparent that the anoxemia test in clinical practice need be employed only when the diagnosis is in doubt. The number of patients falling in this category will not be large among experienced clinicians even though angina without objective evidence of heart disease may represent as many as 25 per cent of patients coming under observation.[108] The test should *not* be performed except under the direct supervision of a physician who has had experience with the test. Careful attention should be given to following the prescribed technique for carrying out the test and judgment should be exercised in the selection of patients following the precautions which have been defined by Levy and by others. It is of particular importance that the patient's resting "control" electrocardiogram be checked immediately before the beginning of the test. For greatest safety it might be advisable that the control electrocardiogram consist of the three standard leads, the unipolar limb leads, and six precordial leads. It has been suggested that since a positive test may occur without pain, an increased precaution would be to follow the tracing of the left precordial lead during the test with a direct visualized record, but this precaution is not necessary for safe execution of the test. The use of an oximeter is a refinement which provides data concerning relative capillary oxygenation. For the most part, however, these last two refinements or modifications are unnecessary in ordinary clinical work and have the disadvantages of adding expense and complicating the execution of the test and requiring additional technical help in making the observations. Whenever pain occurs or whenever any other marked discomfort is indicated by the patient, the test should be promptly discontinued. Nervous and unstable individuals may be unable to cooperate and several attempts might be required before a satisfactory test is possible. Subjective sensations of lack of air, lightheadedness,

headache, hyperventilation, panic, syncope and vasovagal manifestations are the most frequent unpleasant reactions. They are relieved by inhalation of 100 per cent oxygen. The criteria for the interpretation of the results of the test have been established for approximately sea-level barometric pressure.

When the ordinary precautions are taken it appears, from experience of many observers in widely different locations, that the test is safe. It is of special interest to keep in mind that the two reported fatalities resulted from the failure to detect recent myocardial infarction by failure to examine the control record of the patients taken immediately before the test was begun.

In groups of patients with coronary artery disease reported by different investigators, the incidence of positive tests has ranged between 30 to 61 per cent with the usual expectancy of about 50 per cent. A negative test with pain is of questionable significance, but an appreciable number of patients having such tests have either developed a positive one subsequently or have died of heart disease. It should be emphasized that a negative test does not exclude the presence of coronary artery disease, and a significant mortality rate from this disease has been observed in patients who had previously had negative anoxemia tests.[13,67] The results of the test parallel the course and variations in severity of coronary artery disease[45,53] and an individual having a positive test may subsequently have a negative one.[11,45,53] Moreover, patients who have recovered from myocardial infarction may or may not have positive tests. The test, therefore, cannot be used as a guide to prognosis in any individual patient, nor can it be used to predict the future occurrence of myocardial infarction in an individual patient. On the other hand, patients having positive tests as a group have shorter life expectancies than those with negative ones.[67]

The results of exercise and anoxia tests are not invariably similar and are not comparable. Either may be positive when the other one is negative. There is no convincing evidence that one has a marked advantage over the other in its likelihood in detecting evidence of coronary artery disease. Evaluation of the results of exercise tests which have been reported has been made difficult by variations in procedures and in criteria which have been used. This test has the obvious advantages of simplicity and lack of need for special apparatus. It also produces the type of strain which usually causes pain in the anginal patient. It has the disadvantages that the work of the heart may continue for some time after the exercise is discontinued, that there may be delay in recording the electrocardiograms after exercise, and that movement and tachycardia may make measurements of RS-T deviations subject to error. Although five deaths have been reported following the subjection of patients to this test, it is probably not more dangerous than the anoxemia test when it is performed with reasonable precautions. The anoxemia test has the disadvantage that special apparatus is required. On the other hand, the patient is at rest and recumbent, the electrodes are already attached to the patient and, more important, 100 per cent oxygen is immediately available for use if necessary. The electrocardiographic records are easily standardized and interpretation of the results is subject to definite criteria which are generally accepted. The appraisal of possible false-positive tests involves definition and judgment, and they are difficult to evaluate

from the data available in the literature. Fortunately, such tests are not encountered frequently. There are many disease conditions which may be attended by temporary myocardial anoxia and thereby yield significant electrocardiographic responses during the anoxemia test. Among these diseases are anemia, pulmonary diseases, congenital heart disease, valvular heart disease, and myocarditis. Autopsies have not been reported on individuals with positive anoxemia tests attributed to "vegetative imbalance."

At present, patients with positive tests should be regarded as most likely having evidence of coronary insufficiency, the most common cause of which, clinically, is coronary artery disease due to arteriosclerosis of the coronary arteries. Mathers and Levy[66] state that in a follow-up of 150 patients no instance has been found in which a positive reaction occurred in a patient subsequently found to be free of coronary artery disease. More recently Levy[46] has stated: "It is one of the advantages of the anoxemia test, as has been pointed out repeatedly, that false-positive results are not observed. The criteria of a positive result have been clearly defined and have been made sufficiently rigid to exclude such misleading occurrences. . . only a positive test is of diagnostic value."

SUMMARY

The present status of the anoxemia test has been examined and a review of the current literature recorded. The test, a useful one, has been widely employed, and the results analyzed by a large number of observers. Its results are evaluated by definite standard objective criteria of electrocardiographic changes. As further experience is gained, these criteria may be subject to change. The test should be performed at approximately sea-level barometric pressure. It is safe procedure when the prescribed precautions for its performance are followed. It is especially emphasized that the control electrocardiogram should be checked immediately before starting the test. Serious reactions are not likely to result from its judicious use. A positive anoxemia test is indicative of coronary insufficiency at the time when the test is performed. A positive test is not, however, to be considered as a guide of prognosis in an individual case. Anoxemia tests and exercise tests may supplement each other, but they may not be used interchangeably. A negative test does not exclude the presence of coronary artery disease.

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Announcements

Applications for awards available July 1, 1955, will be received by the Life Insurance Medical Research Fund as follows: (1) Postdoctoral research fellowships, until October 29, 1954. Preference is given to those who wish to work on cardiovascular function and disease or related fundamental problems. Minimum stipend $3,500, with allowances for dependents and necessary travel. (2) Grants to institutions in aid of research on cardiovascular problems, until November 15, 1954. Support is available for physiological, biochemical, and other basic work broadly related to cardiovascular problems as well as for clinical research in this field. Further information and application forms may be obtained from the Scientific Director, Life Insurance Medical Research Fund, 345 East 46th Street, New York 17, N. Y.

The 37th Annual Conference of the American Occupational Therapy Association will be held at the Shoreham Hotel, Washington, D. C., October 16 to 22, 1954. The meetings will be as follows:

October 16-17	Preliminary Meetings
October 18-19	Institute—Interpersonal Relations
October 20-21-22	General Conference—Theme: "Capitalize Your Assets"